EP/03/14567

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January 08, 2004

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APPLICATION NUMBER: *60/435,834*
FILING DATE: *December 20, 2002*

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PROVISIONAL APPLICATION FOR PATENT COVER SHEET

A/PA

Case No. DECLE61.001PRF
Date: December 20, 2002

United States Patent and Trademark Office
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ATTENTION: PROVISIONAL PATENT APPLICATION

Sir:

This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 CFR § 1.53(c).

For: **STEROID COMPOUNDS WITH ANTI-TUMOR ACTIVITY**

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Enclosed are:

(X) Specification in 51 pages.

(X) 6 sheets of drawings.

(X) A check in the amount of $160.00 to cover the filing fee is enclosed.

(X) A return prepaid postcard.

(X) The Commissioner is hereby authorized to charge any additional fees which may be required, now or in the future, or credit any overpayment to Account No. 11-1410.

Was this invention made by an agency of the United States Government or under a contract with an agency of the United States Government?

(X) No.

[redacted]

PROVISIONAL APPLICATION FOR PATENT
COVER SHEET

( ) Yes. The name of the U.S. Government agency and the Government contract number are:

(X) Please send correspondence to:

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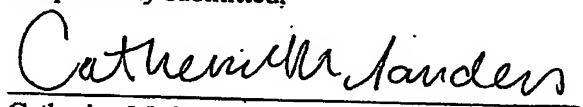
Respectfully submitted,



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CERTIFICATE OF MAILING BY "EXPRESS MAIL"

Attorney Docket No.	:	DECLE61.001PRF
Applicant(s)	:	Braekman et al.
For	:	STEROID COMPOUNDS WITH ANTI-TUMOR ACTIVITY
Agent	:	Catherine M. Sanders
"Express Mail" Mailing Label No.	:	EV 211917227 US
Date of Deposit	:	December 20, 2002

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Transmittal letter; specification in 51 pages; 6 sheets of drawings; Check for Filing Fee; Return Prepaid Postcard

are being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.10 on the date indicated above and are addressed to the United States Patent and Trademark Office, P.O. Box 2327, Arlington, VA 22202.

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STEROID COMPOUNDS WITH ANTI-TUMOR ACTIVITY

Field of the invention

The present invention relates to the medical field. In a first aspect, the present invention relates to novel steroid compounds having a pharmacological activity, in particular an anti-tumor activity. In a second aspect, the present invention relates to a method for preparation of said steroid compounds. The invention further relates in a third aspect to a pharmaceutical composition comprising an effective amount of said steroid compounds. In a fourth aspect, the present invention concerns the use of said steroid compounds as a medicament and the use of said steroid compounds for the preparation of a medicament for the treatment of cancer. In a fifth aspect, the present invention relates to the use of a steroid compound or a pharmaceutical composition comprising said steroid compound according to the invention in the treatment of cancer.

Background of the invention

Cancer develops in a given tissue when some genomic mutation perturbs cell cycle kinetics by increasing cell proliferation or decreasing cell death, or both. This perturbation leads to unrestrained growth of a genomically transformed cell population. Some cells from this transformed cell population may switch to the angiogenic phenotype, enabling them to recruit endothelial cells from the healthy tissue and leading to the sustained growth of the developing neoplastic tumor tissue. Subsequently, some cells migrate from the neoplastic tumor tissue and colonize new tissues, using blood or lymphatic vessels as major routes of migration. This process is also known as the metastatic process.

In practice, most of the agents used today in hospitals to treat cancer patients are drugs, which more or less directly target the cell kinetics, i.e. cell proliferation, of the cancer to be combated. The working mechanism of such anti-cancer drugs essentially relates to the disruption of the development of malignant cells by acting on cell kinetics. These drugs include alkylating agents, intercalating agents, antimetabolites, etc... most of which target DNA or enzymes regulating the DNA duplication and elongation process. These drugs attack the DNA.

A major drawback of these drugs involves that the drugs do not work in a selective manner, i.e. they do not select between normal and neoplastic cells. They are used in accordance with the fact that the DNA of rapidly proliferating cells, i.e. cancer cells, is more sensitive to this type of agents than the DNA of less rapidly proliferating cells, i.e. normal cells. However, rapidly growing tumors are not always tumors exhibiting high levels of cell proliferation. Rapidly growing tumors may also include tumors which exhibit

low levels of cell death compared to the normal cell population from which these tumor cells issue. For these types of rapidly growing tumors, the above-described, non-selective anti-cancer drugs are not effective.

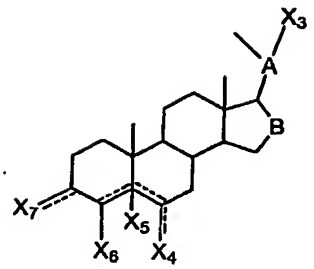
In addition, the great majority of the drugs used in the standard treatment of cancer using the cell kinetics approach have the drawback of being toxic or even highly toxic, i.e. involving many detrimental side-effects on healthy cells, tissues and organs, and this limits their clinical use to a relatively low number of administrations per patient. In addition, several of these compounds must be combined into a poly-chemotherapeutic regimen in order to have any observable effect against cancer. By way of evidence such anti-cancer drug combinations increase detrimentally the toxicity of the treatment and also limit the number of administrations that can be applied.

Some anti-cancer drugs from natural origins, such as e.g. anti-tubulin compounds, using a therapeutic approach different from the cell kinetics approach, have been proposed. Said drugs aim to prevent the migration of cancer cells which escape from the primary tumor tissue and first invade neighbouring tissue therefore establishing metastases. However, the compounds of this type known so far also show major toxic side effects, which limits their use over long periods of treatment.

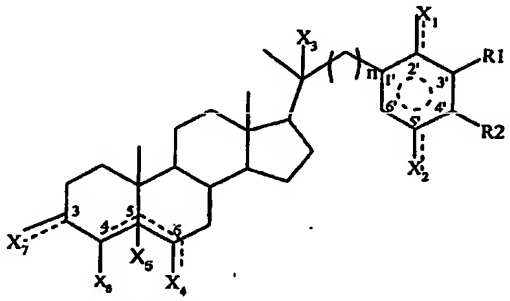
Therefore, there remains an urgent need in the art for finding improved anti-cancer drugs, which overcome at least some of the above-mentioned drawbacks. Consequently, it is a general object of the invention to provide improved anti-cancer drugs. More in particular, it is an object of the present invention to provide novel anti-cancer drugs and methods for synthesizing these. It is still another object of the invention to provide intermediate compounds as a result of the aforementioned synthesis methods, which have a pharmaceutical utility, e.g. in the treatment of cancer.

Summary of the invention

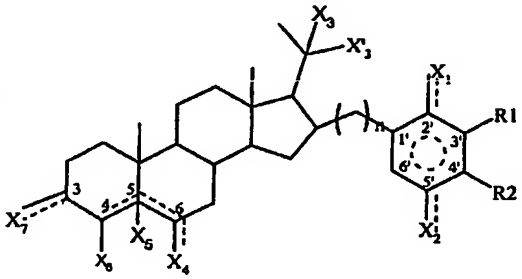
In a first aspect the present invention relates to steroid compounds having the below given basic structure and being substituted in positions A or B.



In particular, the present invention relates to steroid compounds of the formula IA or formula IB or a pharmaceutically acceptable salt thereof,



formula IA



formula IB

wherein X_1, X_2, R_1 and R_2 are independently selected from the group comprising oxo, hydrogen, hydroxyl, oxyalkyl, alkyl, alkenyl, alkynyl, alkyloxy, alkyloxyalkyl, alkylthioalkyl, alkoxycarbonyl, alkylthiocarbonyl, alkanoyl, cycloalkylalkyl, cycloalkylcarbonyl, cycloalkylalkanoyl, cycloalkylthiocarbonyl, cycloalkylalkoxycarbonyl, cycloalkylalkoxythiocarbonyl, cycloalkylthioalkyl, alkylcarbonyloxyalkyl, cycloalkylcarbonyloxyalkyl, silyloxyalkyl, aralkyl, arylalkenyl, arylcarbonyl, aryloxycarbonyl, arylthiocarbonyl, aralkoxycarbonyl, arylalkylthiocarbonyl, aryloxyalky, arylthioalkyl, haloalkyl, hydroxyalkyl, aralkanoyl, aroyl, aryloxycarbonylalkyl, aryloxyalkanoyl, carboxyl, alkenylcarbonyl, alkynylcarbonyl, Het^1, Het^1alkyl, Het^1oxyalkyl, Het^1aryl, Het^1aralkyl, Het^1cycloalkyl, Het^1alkoxycarbonyl, Het^1alkylthiocarbonyl, Het^1oxycarbonyl, Het^1thiocarbonyl, Het^1alkanoyl, Het^1aralkanoyl, Het^1aryloxyalkyl, Het^1alkyloxyalkyl, Het^1arylthioalkyl, Het^1aryloxycarbonyl, Het^1aralkoxycarbonyl, Het^1aroyl, Het^1oxyalkylcarbonyl, Het^1alkyloxyalkylcarbonyl, Het^1aryloxyalkylcarbonyl, Het^1carbonyloxyalkyl, Het^1alkylcarbonyloxyalkyl, Het^1aralkylcarbonyloxyalkyl, Het^2alkyl, Het^2oxyalkyl, Het^2alkyloxyalkyl, Het^2aralkyl, Het^2carbonyl, Het^2oxycarbonyl, Het^2thiocarbonyl, Het^2alkanoyl, Het^2alkylthiocarbonyl, Het^2alkoxycarbonyl, Het^2aralkanoyl, Het^2aralkoxycarbonyl, Het^2aryloxycarbonyl, Het^2aroyl, Het^2aryloxyalkyl, Het^2arylthioalkyl, Het^2oxyalkylcarbonyl, Het^2alkyloxyalkylcarbonyl, Het^2aryloxyalkylcarbonyl,

Het^2carbonyloxyalkyl, Het^2alkylcarbonyloxyalkyl, Het^2aralkylcarbonyloxyalkyl, cyano, $CR^3=NR^4$, $CR^3=N(OR^4)$, aminocarbonyl, aminoalkanoyl, aminoalkyl, optionally substituted by one or more substituents independently selected from the group comprising alkyl, aralkyl, aryl, Het^1, Het^2, cycloalkyl, alkyloxy, alkyloxycarbonyl, carboxyl, aminocarbonyl, mono- or di(alkyl)aminocarbonyl, aminosulfonyl, alkylS(=O)$_t$, hydroxy, cyano, halogen or amino optionally mono- or disubstituted wherein the substituents are independently selected from the group comprising alkyl, aryl, aralkyl, aryloxy, arylamino, arylthio, aryloxyalkyl, arylaminoalkyl, aralkoxy, alkylthio, alkoxy, aryloxyalkoxy, aylaminoalkoxy, aralkylamino, aryloxyalkylamino, arylaminoalkylamino, arylthioalkoxy, arylthioalkylamino, aralkylthio, aryloxyalkylthio, arylaminoalkylthio, arylthioalkylthio, alkylamino, cycloalkyl, cycloalkylalkyl, Het^1, Het^2, Het^1alkyl, Het^2alkyl, Het^1amino, Het^2amino, Het^1alkylamino, Het^2alkylamino, Het^1thio, Het^2thio, Het^1alkylthio, Het^2alkylthio, Het^1oxy and Het^2oxy, OR^3, SR^3, $SO_2NR^3R^4$, $SO_2N(OH)R^3$, CN, $CR^3=NR^4$, $S(O)R^3$, SO_2R^3, $CR^3=N(OR^4)$, N_3, NO_2, NR^3R^4, $N(OH)R^3$, $C(O)R^3$, $C(S)R^3$, CO_2R^3, $C(O)SR^3$, $C(O)NR^3R^4$, $C(S)NR^3R^4$, $C(O)N(OH)R^4$, $C(S)N(OH)R^3$, $NR^3C(O)R^4$, $NR^3C(S)R^4$, $N(OH)C(O)R^4$, $N(OH)C(S)R^3$, $NR^3CO_2R^4$, $NR^3C(O)NR^4R^5$, and $NR^3C(S)NR^4R^5$, $N(OH)CO_2R^3$, $NR^3C(O)SR^4$, $N(OH)C(O)NR^3R^4$, $N(OH)C(S)NR^3R^4$, $NR^3C(O)N(OH)R^4$, $NR^3C(S)N(OH)R^4$, $NR^3SO_2R^4$, $NHSO_2NR^3R^4$, $NR^3SO_2NHR^4$, $P(O)(OR^3)(OR^4)$, wherein t is an integer between 1 and 2 and R^3, R^4 and R^5 are each independently selected from the group comprising hydrogen, hydroxyl, alkyl, alkenyl, alkynyl, aminoalkyl, aminoaryl, alkylcarbonylamino, arylcarbonylamino alkylthiocarbonylamino and arylthiocarbonylamino;

wherein X_3 participates together with X_3' to an oxo functional group, or wherein X_3 is selected from the group comprising hydrogen, hydroxyl, sulfur, oxyalkyl, oxycarbonyl, alkyl, Het^1alkyl, alkenyl, alkynyl, aminoalkyl, aminoacyl, alkylcarbonylamino, alkylthiocarbonylamino, alkyloxycarbonyl optionally substituted by one or more substituents independently selected from the group comprising alkyl, aralkyl, aryl, Het^1, Het^2, cycloalkyl, alkyloxy, alkyloxycarbonyl, carboxyl and aminocarbonyl; and X_3' is selected from the group comprising hydrogen, alkyl, aryl, aralkyl, and optionally substituted by one or more substituents independently selected from the group comprising alkyl, aralkyl, aryl, Het^1, Het^2, cycloalkyl, alkyloxy, alkyloxycarbonyl, carboxyl, aminocarbonyl, mono- or di(alkyl)aminocarbonyl, aminosulfonyl, alkylS(=O)$_t$, hydroxy, cyano, halogen or amino optionally mono- or disubstituted wherein the substituents are independently selected from the group comprising alkyl, aryl, aralkyl, aryloxy, arylamino, arylthio, aryloxyalkyl, arylaminoalkyl, aralkoxy, alkylthio, alkoxy, aryloxyalkoxy, aylaminoalkoxy, aralkylamino, aryloxyalkylamino, arylaminoalkylamino, arylthioalkoxy, arylthioalkylamino, aralkylthio, aryloxyalkylthio, arylaminoalkylthio, arylthioalkylthio, alkylamino, cycloalkyl and cycloalkylalkyl;

wherein X_4 and X_7 are independently selected from the group comprising hydrogen, oxygen, halogen, oxo, carbonyl, thiocarbonyl, hydroxyl, alkyl, aryl, Het^1alkyl, Het^1aryl, alkenyl, alkynyl, hydroxyalkyl, hydroxycarbonyl, hydroxycarbonylalkyl, hydroxycarbonylaryl, hydroxycarbonyloxyalkyl and hydroxycarbonyloxyaryl; aminocarbonyl, mono- or di(alkyl)aminocarbonyl, aminosulfonyl, alkylS(=O)$_t$, hydroxy, aminoalkyl, aminoaryl, cyano, halogen or amino optionally mono- or disubstituted wherein the substituents are independently selected from the group comprising alkyl, aryl, aralkyl, aryloxy, arylamino, arylthio, aryloxyalkyl, arylaminoalkyl, aralkoxy, alkylthio, alkoxy, aryloxyalkoxy, aylaminoalkoxy, aralkylamino, aryloxyalkylamino, arylaminoalkylamino, arylthioalkoxy, arylthioalkylamino, aralkylthio, aryloxyalkylthio, arylaminoalkylthio, arylthioalkylthio, alkylamino, Het^1, Het^2, alkyloxycarbonyl, carboxyl, aminocarbonyl, cycloalkyl and cycloalkylalkyl,

wherein X_5 participates to a double bond between the carbon atoms in position 4 and 5 or between carbon atoms in positions 5 and 6, and X_6 is independently selected from the group comprising hydrogen, hydroxyl and hydroxyalkyl, or

wherein X_5 and X_6 are independently selected from the group comprising halogen hydrogen, hydroxyl, hydroxyalkyl, aminoalkyl, aminoaryl, optionally substituted by one or more substituents independently selected from the group comprising alkyl, aralkyl, aryl, Het^1, Het^2, cycloalkyl, alkyloxy, alkyloxycarbonyl, carboxyl, aminocarbonyl, and

wherein n is an integer between 0 and 10.

The present invention provides novel steroid compounds that have anti-tumor activity and that are consequently very suitable for use in all kind of therapeutic applications as described below.

In a second aspect, the present invention relates to a method for synthesizing said steroid compounds.

In addition, the present invention further relates to pharmaceutical compositions comprising the above-described compounds. Furthermore, the present invention relates to steroid compounds for use as a medicament and for use in the preparation of a medicament for the treatment of diseases associated with cell proliferation, in particular for treatment of cancer. The present invention further relates to the use of the above-described compounds or a pharmaceutical composition comprising said compounds in the treatment of cancer.

Detailed description of the figures

Figure 1 represents an example of a reaction scheme for preparing a steroid compound according to the invention.

Figures 2 to 5 represent the anti-tumor activity of different steroid compounds according to the invention on six human cancer cell lines. Figure 2, 3, 4 and 5 represent the anti-tumor activity of compounds UBS881, UBS1664, UBS1740 and UBS1819, respectively.

Figure 6 compares the cytotoxic and anti-tumor activity of different compounds according to the invention, in particular compounds UBS881, UBS1664, UBS1740 and UBS1819 on six human cancer cell lines.

Detailed description of the invention

Steroid compounds according to the invention

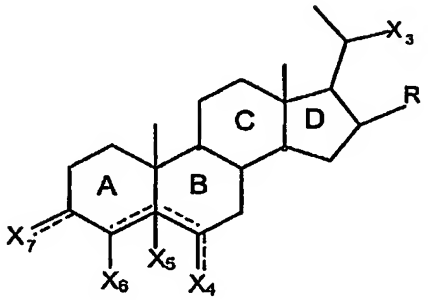
A lot of steroids compounds are described in the literature. These compounds have various biological activities. For example, WO 96/10031 and WO 98/14194 describe steroid derivatives as neurochemical stimulators of a specific neuroepithelial receptor to alleviate symptoms of anxiety.

The present invention now relates to novel steroid compounds showing anti-tumor activity. According to the present invention the term "anti-tumor activity", refers to the *in vitro* as well as *in vivo* anti-tumor effects exerted by the steroid compounds according to the invention. The anti-tumor effects essentially include but are not limited to a dramatic decrease of cell growth and a pro-apoptotic effect. Importantly, the steroid compounds according to the invention exhibits anti-tumor activity on a large number of cancer types, such as but not limited to glioma cancer, colon cancer, lung cancer and bladder cancer amongst others.

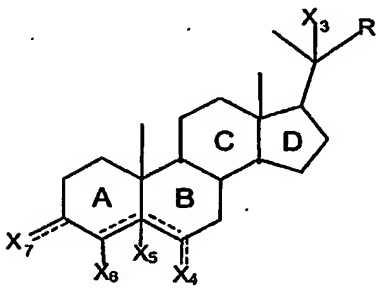
Importantly, the steroid compounds according to the invention also have an anti-migratory effect. Migration refers to the process whereby cells migrate from the neoplastic tumor tissue and colonize new tissues, using blood or lymphatic vessels as major routes of migration. This process is also known as the metastatic process. According to the present invention the term "anti-migratory", refers to the ability of compounds according to the invention to stop the migration of cells away from the neoplastic tumor tissue and thus reduces the colonization of new tissues by these cells.

The term "steroid" as used herein is intended to mean compounds having a perhydrogenated cyclopentanophenanthrene nucleus. The compounds according to the

invention, represented by the general formula given below, have four rings, represented by the letters A to D.



general formula IA



general formula IB

Whenever the term "substituted" is used in the present invention, it is meant to indicate that one or more hydrogens on the atom indicated in the expression using "substituted" is replaced with a selection from the indicated group, provided that the indicated atom's normal valency is not exceeded, and that the substitution results in a chemically stable compound, i.e. a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into a therapeutic agent.

As used herein, the term "halo" or "halogen" as a group or part of a group is generic for fluoro, chloro, bromo or iodo.

The term "alkyl", alone or in combination, means straight and branched chained saturated hydrocarbon radicals containing from 1 to 10 carbon atoms, preferably from 1 to 8 carbon atoms, more preferably 1 to 6 carbon atoms. Examples of such radicals include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, 2-methylbutyl, pentyl, iso-amyl, hexyl, 3-methylpentyl, octyl and the like.

The term "alkenyl", alone or in combination, defines straight and branched chained hydrocarbon radicals containing from 2 to about 18 carbon atoms, preferably from 2 to 8 carbon atoms, more preferably 2-6 carbon atoms containing at least one double bond such as, for example, ethenyl, propenyl, butenyl, pentenyl, hexenyl and the like.

The term "alkynyl", alone or in combination, defines straight and branched chained hydrocarbon radicals having from 2 to 10 carbon atoms containing at least one triple bond,

more preferably from 2 to about 6 carbon atoms. Examples of alkynyl radicals include ethynyl, propynyl, (propargyl), butynyl, pentynyl, hexynyl and the like.

The term "cycloalkyl" alone or in combination, means a saturated or partially saturated monocyclic, bicyclic or polycyclic alkyl radical wherein each cyclic moiety contains from about 3 to about 8 carbon atoms, more preferably from about 3 to about 7 carbon atoms. Examples of monocyclic cycloalkyl radicals include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl and the like. Examples of polycyclic cycloalkyl radicals include decahydronaphthyl, bicyclo [5.4.0] undecyl, adamantyl, and the like.

The term "cycloalkylalkyl" means an alkyl radical as defined herein, in which at least one hydrogen atom on the alkyl radical is replaced by a cycloalkyl radical as defined herein. Examples of such cycloalkylalkyl radicals include cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl, cyclohexylmethyl, 1-cyclopentylethyl, 1-cyclohexylethyl, 2-cyclopentylethyl, 2-cyclohexylethyl, cyclobutylpropyl, cyclopentylpropyl, 3-cyclopentylbutyl, cyclohexylbutyl and the like.

The term "aryl" alone or in combination, is meant to include phenyl and naphtyl which both may be optionally substituted with one or more substituents independently selected from alkyl, alkoxy, halogen, hydroxy, amino, nitro, cyano, haloalkyl, carboxy, alkoxycarbonyl, cycloalkyl, Het^1, amido, optionally mono- or disubstituted aminocarbonyl, methylthio, methylsulfonyl, and phenyl optionally substituted with one or more substituents selected from C_{1-6}alkyl, C_{1-6}alkyloxy, halogen, hydroxy, optionally mono- or disubstituted amino, nitro, cyano, haloC_{1-6}alkyl, carboxyl, C_{1-6}alkoxycarbonyl, C_{3-7}cycloalkyl, Het^1, optionally mono- or disubstituted aminocarbonyl, methylthio and methylsulfonyl; whereby the optional substituents on any amino function are independently selected from alkyl, alkyloxy, Het^1, Het^1alkyl, Het^1alkyl, Het^1oxy, Het^1oxyalkyl, phenyl, phenyloxy, phenyloxyalkyl, phenylalkyl, alkyloxycarbonylamino, amino, and aminoalkyl whereby each of the amino groups may optionally be mono- or where possible di-substituted with alkyl. Examples of aryl includes phenyl, p-tolyl, 4-methoxyphenyl, 4-(tert-butoxy)phenyl, 3-methyl-4-methoxyphenyl, 4-fluorophenyl, 4-chlorophenyl, 3-nitrophenyl, 3-aminophenyl, 3-acetamidophenyl, 4-acetamidophenyl, 2-methyl-3-acetamidophenyl, 2-methyl-3-aminophenyl, 3-methyl-4-aminophenyl, 2-amino-3-methylphenyl, 2,4-dimethyl-3-aminophenyl, 4-hydroxyphenyl, 3-methyl-4-hydroxyphenyl, 1-naphthyl, 2-naphthyl, 3-amino-1-naphthyl, 2-methyl-3-amino-1-naphthyl, 6-amino-2-naphthyl, 4,6-dimethoxy-2-naphthyl and the like.

The term "aralkyl" alone or in combination, means an alkyl as defined herein, wherein an alkyl hydrogen atom is replaced by an aryl as defined herein. Examples of aralkyl radicals include benzyl, phenethyl, dibenzylmethyl, methylphenylmethyl, 3- (2-naphthyl)-butyl, and the like.

As used herein, the term "oxo" or "=O" forms a carbonyl moiety with the carbon atom to which it is attached. As used herein, the term "carboxyl" or "-COOH" is an acid moiety whereby the carbon atom binds to the carbon atom to which it is attached.

The term "haloalkyl" alone or in combination, means an alkyl radical having the meaning as defined above wherein one or more hydrogens are replaced with a halogen, preferably, chloro or fluoro atoms, more preferably fluoro atoms. Examples of such haloalkyl radicals include chloromethyl, 1-bromoethyl, fluoromethyl, difluoromethyl, trifluoromethyl, 1,1,1-trifluoroethyl and the like.

The term "Het^1" alone or in combination, is defined as a saturated or partially unsaturated monocyclic, bicyclic or polycyclic heterocycle having preferably 3 to 12 ring members, more preferably 5 to 10 ring members and more preferably 5 to 6 ring members, which contains one or more heteroatom ring members selected from nitrogen, oxygen or sulfur and which is optionally substituted on one or more carbon atoms by alkyl, alkyloxy, halogen, hydroxy, oxo, optionally mono- or disubstituted amino, nitro, cyano, haloalkyl, carboxyl, alkoxycarbonyl, cycloalkyl, optionally mono- or disubstituted aminocarbonyl, methylthio, methylsulfonyl, aryl and a saturated or partially unsaturated monocyclic, bicyclic or tricyclic heterocycle having 3 to 12 ring members which contains one or more heteroatom ring members selected from nitrogen, oxygen or sulfur and whereby the optional substituents on any amino function are independently selected from alkyl, alkyloxy, Het^2, Het^2alkyl, Het^2oxy, Het^2oxyalkyl, aryl, aryloxy, aryloxyalkyl, aralkyl, alkyloxycarbonylamino, amino, and aminoalkyl whereby each of the amino groups may optionally be mono- or where possible di-substituted with alkyl.

The term "Het^2" as a group or part of a group is defined as an aromatic monocyclic, bicyclic or tricyclic heterocycle having preferably 3 to 12 ring members, more preferably 5 to 10 ring members and more preferably 5 to 6 ring members, which contains one or more heteroatom ring members selected from nitrogen, oxygen or sulfur and which is optionally substituted on one or more carbon atoms by alkyl, alkyloxy, halogen, hydroxy, optionally mono- or disubstituted amino, nitro, cyano, haloalkyl, carboxyl, alkoxycarbonyl, cycloalkyl, optionally mono- or disubstituted aminocarbonyl, methylthio, methylsulfonyl, aryl, Het^1 and

[redacted]

an aromatic monocyclic, bicyclic or tricyclic heterocycle having 3 to 12 ring members; whereby the optional substituents on any amino function are independently selected from alkyl, alkyloxy, Het[1], Het[1]alkyl, Het[1]oxy, Het[1]oxyalkyl, aryl, aryloxy, aryloxyalkyl, aralkyl, alkyloxycarbonylamino, amino, and aminoalkyl whereby each of the amino groups may optionally be mono- or where possible di-substituted with alkyl.

The term "alkoxy" or "alkyloxy", alone or in combination, means an alkyl ether radical wherein the term alkyl is as defined above. Examples of suitable alkyl ether radicals include methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, iso-butoxy, sec-butoxy, tert-butoxy, hexanoxy and the like.

The term "arylthioalkoxy" means alkoxy as defined herein, wherein an alkyl hydrogen atom is replaced by an arylthio as defined herein. Examples of (arylthio) alkoxy radicals include 2- (phenylthio)-ethoxy, and the like.

The term "alkanoyl" or "alkylcarbonyl", alone or in combination, means an acyl radical derived from an alkanecarboxylic acid, examples of which include acetyl, propionyl, butyryl, valeryl, 4-methylvaleryl, and the like.

The term "alkylamino" means an alkyl amine radical, wherein the term "alkyl" is defined as above. Examples of alkylamino radicals include methylamino ($NHCH_3$), ethylamino ($NHCH_2CH_3$), n-propylamino, isopropylamino, n-butylamino, isobutylamino, sec-butylamino, tert-butylamino, n-hexylamino, and the like.

The term "alkylthio" means an alkyl thioether radical, wherein the term "alkyl" is defined as above. Examples of alkylthio radicals include methylthio (SCH_3), ethylthio (SCH_2CH_3), n-propylthio, isopropylthio, n-butylthio, isobutylthio, sec-butylthio, tert-butylthio, n-hexylthio, and the like.

The term "aminoalkanoyl" means an acyl group derived from an amino-substituted alkylcarboxylic acid wherein the amino group can be a primary, secondary or tertiary amino group containing substituents selected from alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl radicals and the like.

The term "aminocarbonyl" alone or in combination, means an amino-substituted carbonyl (carbamoyl) group wherein the amino group can be a primary, secondary or tertiary amino

group containing substituents selected from alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl radicals and the like.

The term "aralkanoyl" means an acyl radical derived from an aryl-substituted alkanecarboxylic acid such as phenylacetyl, 3-phenylpropionyl (hydrocinnamoyl), 4-phenylbutyryl, (2-naphthyl)acetyl, 4-chlorohydrocinnamoyl, 4-aminohydrocinnamoyl, 4-methoxyhydrocinnamoyl, and the like.

The term "aralkoxy" means alkoxy as defined herein, wherein an alkyl hydrogen atom is replaced by an aryl as defined herein. Examples of aralkoxy radicals include 2-phenylethoxy, 2-phenyl-1-propoxy, and the like.

The term "aralkoxycarbonyl", alone or in combination, means a radical of the formula aralkyl-O-C(O)- in which the term "aralkyl" has the significance given above. Examples of an aralkoxycarbonyl radical are benzyloxycarbonyl and 4-methoxyphenylmethoxycarbonyl.

The term "aralkylamino" means alkylamino as defined herein, wherein an alkyl hydrogen atom is replaced by an aryl as defined herein. Examples of aralkylamino radicals include 2-phenethylamino, 4-phenyl-n-butylamino, and the like.

The term "aralkylthio" means alkylthio as defined herein, wherein an alkyl hydrogen atom is replaced by an aryl as defined herein. Examples of aralkylthio radicals include 3-phenyl-2-propylthio, 2- (2-naphthyl)-ethylthio, and the like.

The term "aroyl" means an acyl radical derived from an arylcarboxylic acid, aryl having the meaning given above. Examples of such arylcarboxylic acid radicals include substituted and unsubstituted benzoic or naphthoic acid such as benzoyl, 4-chlorobenzoyl, 4-carboxybenzoyl, 4-(benzyloxycarbonyl)benzoyl, 1-naphthoyl, 2-naphthoyl, 6-carboxy-2 naphthoyl, 6-(benzyloxycarbonyl)-2-naphthoyl, 3-benzyloxy-2-naphthoyl, 3-hydroxy-2-naphthoyl, 3-(benzyloxyformamidol-2-naphthoyl, and the like.

The term "arylaminoalkoxy" means alkoxy as defined herein, wherein an alkyl hydrogen atom is replaced by an arylamino as defined herein. Examples of (arylamino) alkoxy radicals include 2- (phenylamino)-ethoxy, 2- (2- naphthylamino)-1-butoxy, and the like.

[redacted]

The term "arylaminoalkyl" means alkyl as defined herein, wherein an alkyl hydrogen atom is replaced by an arylamino as defined herein. Examples of arylaminoalkyl radicals include phenylaminoethyl, 4- (3-methoxyphenylamino)- 1-butyl, and the like.

The term "arylaminoalkylamino" means alkylamino as defined herein, wherein an alkyl hydrogen atom is replaced by an arylamino as defined herein. Examples of (arylamino) alkylamino radicals include 3- (naphthylamino)-propylamino, 4- (phenylamino)-1-butylamino, and the like.

The term "arylaminoalkylthio" means alkylthio as defined herein, wherein an alkyl hydrogen atom is replaced by an arylamino as defined herein. Examples of (arylamino) alkylthio radicals include 2- (phenylamino)- ethylthio, 3- (2-naphthylamino)-n-propylthio, and the like.

The term "aryloxy" means a radical of the formula aryl-O-in which the term aryl has the significance given above.

The term "aryloxyalkanoyl" means an acyl radical of the formula aryl-O-alkanoyl wherein aryl and alkanoyl have the meaning given above.

The term "aryloxyalkoxy" means alkoxy as defined herein, wherein an alkyl hydrogen atom is replaced by an aryloxy as defined herein. Examples of (aryloxy) alkoxy radicals include 2-phenoxyethoxy, 4- (3-aminophenoxy)-1- butoxy, and the like.

The term "aryloxyalkyl" means alkyl as defined herein, wherein an alkyl hydrogen atom is replaced by an aryloxy as defined herein. Examples of aryloxyalkyl radicals include phenoxyethyl, 4- (3-aminophenoxy)-l-butyl, and the like.

The term "aryloxyalkylamino" means alkylamino as defined herein, wherein an alkyl hydrogen atom is replaced by an aryloxy as defined herein. Examples of (aryloxy) alkylamino radicals include 3-phenoxy-npropylamino, 4-phenoxybutylamino, and the like.

The term "aryloxyalkylthio" means alkylthio as defined herein, wherein an alkyl hydrogen atom is replaced by an aryloxy as defined herein. Examples of (aryloxy) alkylthio radicals include 3-phenoxypropylthio, 4 (2-fluorophenoxy)-butylthio, and the like.

[redacted]

The term "arylthioalkylamino" means alkylamino as defined herein, wherein an alkyl hydrogen atom is replaced by an arylthio as defined herein. Examples of (arylthio) alkylamino radicals include 2- (phenylthio)- ethylamino, and the like.

The term "arylthioalkylthio" means alkylthio as defined herein, wherein an alkyl hydrogen atom is replaced by an arylthio as defined herein. Examples of (arylthio) alkylthio radicals include 2- (naphthylthio)- ethylthio, 3- (phenylthio)-propylthio, and the like.

The term "cycloalkylalkoxycarbonyl" means an acyl group derived from a cycloalkylalkoxycarboxylic acid of the formula cycloalkylalkyl-O-COOH wherein cycloalkylalkyl has the meaning given above.

The term "cycloalkylcarbonyl" means an acyl group derived from a monocyclic or bridged cycloalkanecarboxylic acid such as cyclopropylcarbonyl, cyclohexylcarbonyl, adamantylcarbonyl, and the like, or from a benz-fused monocyclic cycloalkanecarboxylic acid which is optionally substituted by one or more substituents selected from alkyl, alkoxy, halogen, hydroxy, amino, nitro, cyano, haloalkyl, carboxy, alkoxycarbonyl, cycloalkyl, heterocycloalkyl, alkanoylamino, amido, mono and dialkyl substituted amino, mono and dialkyl substituted amido and the like, such as 1,2,3,4-tetrahydro-2-naphthoyl, 2-acetamido-1,2,3,4-tetrahydro-2-naphthoyl.

The term "Het^2alkoxy" means alkoxy as defined herein, wherein an alkyl hydrogen atom is replaced by a Het^2 as defined herein. Examples of Het^2alkoxy radicals include 2-pyridylmethoxy, 4- (l-imidazolyl)-butoxy, and the like.

The term "Het^2alkyl" means alkyl as defined herein, wherein an alkyl hydrogen atom is replaced by a Het^2 as defined herein. Examples of Het^2alkyl radicals include 2-pyridylmethyl, 3- (4-thiazolyl)-propyl, and the like.

The term "Het^2alkylamino" means alkylamino as defined herein, wherein an alkyl hydrogen atom is replaced by a Het^2 as defined herein. Examples of Het^2alkylamino radicals include 4-pyridylmethylamino, 3 (2-furanyl)-propylamino, and the like.

The term "Het^2alkylthio" means alkylthio as defined herein, wherein an alkyl hydrogen atom is replaced by a Het^2 as defined herein. Examples of Het^2alkylthio radicals include 3-pyridylmethylthio, 3 (4-thiazolyl)-propylthio, and the like.

The term "Het^{2}amino" means Het^2 as defined herein, wherein a hydrogen atom on the Het^2 ring is replaced by a nitrogen. Het^{2}amino radicals include, for example, 4-thiazolylamino, 2-pyridylamino, and the like.

The term "Het^{2}oxy" means Het^2 as defined herein, wherein a hydrogen atom on the Het^2 ring is replaced by an oxygen. Het^{2}oxy radicals include, for example, 4-pyridyloxy, 5-quinolyloxy, and the like.

The term "Het^{2}oxycarbonyl" means an acyl radical derived from a carbonic acid represented by Het^2-O-COOH wherein Het^2 has the meaning given above.

The term "Het^{2}thio" means Het^2 as defined herein, wherein a hydrogen atom on the Het^2 ring is replaced by a sulfur. Het^{2}thio radicals include, for example, 3-pyridylthio, 3-quinolylthio, 4-imidazolylthio, and the like.

The term "Het^{1}alkanoyl" is an acyl radical derived from a Het^1-substituted alkylcarboxylic acid wherein Het^1 has the meaning given above.

The term "Het^{1}alkoxycarbonyl" means an acyl group derived from Het^1-O-COOH wherein Het^1 is as defined above.

As used herein before, the term "one or more" covers the possibility of all the available C-atoms, where appropriate, to be substituted, preferably, one, two or three. When any variable, e.g. halogen or alkyl, occurs more than one time in any constituent, each definition is independent.

Whenever used in the present invention the term "compounds of the invention" or "steroid compounds" or a similar term is meant to include the compounds of general formula IA and formula IB and any subgroup thereof. This term also refers to the compounds as depicted in Table A and their *N*-oxides, salts, stereoisomeric forms, racemic mixtures, pro-drugs, esters and metabolites, as well as their quaternized nitrogen analogues. The *N*-oxide forms of said compounds are meant to comprise compounds wherein one or several nitrogen atoms are oxidized to the so-called *N*-oxide.

The term "pro-drug" as used herein means the pharmacologically acceptable derivatives such as esters, amides and phosphates, such that the resulting *in vivo* biotransformation product of the derivative is the active drug. The reference by Goodman and Gilman (The

Pharmacological Basis of Therapeutics, 8th Ed, McGraw-Hill, Int. Ed. 1992, "Biotransformation of Drugs", p 13-15) describing pro-drugs generally is hereby incorporated. Pro-drugs of the compounds of the invention can be prepared by modifying functional groups present in said component in such a way that the modifications are cleaved, either in routine manipulation or *in vivo*, to the parent component. Typical examples of pro-drugs are described for instance in WO 99/33795, WO 99/33815, WO 99/33793 and WO 99/33792 all incorporated herein by reference. Pro-drugs are characterized by increased bio-availability and are readily metabolized into the active inhibitors *in vivo*.

The compounds according to the invention may also exist in their tautomeric forms. Such forms, although not explicitly indicated in the compounds described herein, are intended to be included within the scope of the present invention.

The term stereochemically isomeric forms of the analogues according to the invention, as used herein, defines all possible compounds made up of the same atoms bonded by the same sequence of bonds but having different three-dimensional structures which are not interchangeable, which the compounds of the present invention may possess. Unless otherwise mentioned or indicated, the chemical designation of a compound herein encompasses the mixture of all possible stereochemically isomeric forms, which said compound may possess. Said mixture may contain all diastereomers and/or enantiomers of the basic molecular structure of said compound. All stereochemically isomeric forms of the compounds of the invention either in pure form or in admixture with each other are intended to fall within the scope of the present invention.

For therapeutic use, the salts of the compounds according to the invention, are those wherein the counter-ion is pharmaceutically or physiologically acceptable.

The pharmaceutically acceptable salts of the compounds according to the invention, i.e. in the form of water-, oil-soluble, or dispersible products, include the conventional non-toxic salts or the quaternary ammonium salts which are formed, e.g., from inorganic or organic acids or bases. Examples of such acid addition salts include acetate, adipate, alginate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, citrate, camphorate, camphorsulfonate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, fumarate, glucoheptanoate, glycerophosphate, hemisulfate, heptanoate, hexanoate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethanesulfonate, lactate, maleate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, oxalate, pamoate, pectinate,

persulfate, 3-phenylpropionate, picrate, pivalate, propionate, succinate, tartrate, thiocyanate, tosylate, and undecanoate. Base salts include ammonium salts, alkali metal salts such as sodium and potassium salts, alkaline earth metal salts such as calcium and magnesium salts, salts with organic bases such as dicyclohexylamine salts, N-methyl-D-glucamine, and salts with amino acids such a sarginine, lysine, and so forth. Also, the basic nitrogen-containing groups may be quaternized with such agents as lower alkyl halides, such as methyl, ethyl, propyl, and butyl chloride, bromides and iodides; dialkyl sulfates like dimethyl, diethyl, dibutyl; and diamyl sulfates, long chain halides such as decyl, lauryl, myristyl and stearyl chlorides, bromides and iodides, aralkyl halides like benzyl and phenethyl–bromides and others. Other pharmaceutically acceptable salts include the sulfate salt ethanolate and sulfate salts.

In a preferred embodiment the present invention relates to a steroid compound of the formula IA or formula IB as indicated above, or a pharmaceutically acceptable salt thereof,

wherein X_1, X_2, R_1 and R_2 is selected from the group comprising hydrogen, hydroxyl, oxyalkyl, oxo, alkyl, alkenyl, alkynyl, alkyloxy, alkyloxyalkyl, alkylthioalkyl, alkoxycarbonyl, alkylthiocarbonyl, alkanoyl, cycloalkylalkyl, cycloalkylcarbonyl, cycloalkylalkanoyl, cycloalkylthiocarbonyl, cycloalkylalkoxycarbonyl, cycloalkylalkoxythiocarbonyl, cycloalkylthioalkyl, alkylcarbonyloxyalkyl, cycloalkylcarbonyloxyalkyl, silyloxyalkyl, aralkyl, arylalkenyl, arylcarbonyl, aryloxycarbonyl, arylthiocarbonyl, aralkoxycarbonyl, arylalkylthiocarbonyl, aryloxyalky, arylthioalkyl, haloalkyl, hydroxyalkyl, aralkanoyl, aroyl, aryloxycarbonylalkyl, aryloxyalkanoyl, carboxyl, alkenylcarbonyl and alkynylcarbonyl;

wherein X_3 participates together with X_3' to an oxo functional group, or wherein X_3 is selected from the group comprising hydrogen, hydroxyl, sulfur, oxyalkyl, oxycarbonyl alkyl, Het^1alkyl, alkenyl, alkynyl, aminoalkyl, aminoacyl, alkylcarbonylamino, alkylthiocarbonylamino, alkyloxycarbonyl optionally substituted by one or more substituents independently selected from the group comprising alkyl, aralkyl, aryl, Het^1, Het^2, cycloalkyl, alkyloxy, alkyloxycarbonyl, carboxyl and aminocarbonyl; and X_3' is selected from the group comprising hydrogen, alkyl, aryl, aralkyl;

wherein X_4 and X_7 are independently selected from the group comprising hydrogen, oxygen, oxo, carbonyl, thiocarbonyl, hydroxyl, alkyl, aryl, Het^1alkyl, Het^1aryl, alkenyl, alkynyl, hydroxyalkyl, hydroxycarbonyl, hydroxycarbonylalkyl, hydroxycarbonylaryl, and hydroxycarbonyloxyalkyl;

wherein X_5 participates to a double bond between the carbon atoms in position 4 and 5 or between carbon atoms in position 5 and 6, and X_6 is independently selected from the group comprising hydrogen, hydroxyl, and hydroxyalkyl, or wherein X_5 and X_6 are

independently selected from the group comprising hydrogen, hydroxyl, hydroxyalkyl, aminoalkyl, aminoaryl, optionally substituted by one or more substituents independently selected from the group comprising alkyl, aralkyl, aryl, Het^1, Het^2, cycloalkyl, alkyloxy, alkyloxycarbonyl, carboxyl, aminocarbonyl, and

wherein n is an integer between 0 and 5.

In a more preferred embodiment, the present invention relates to a steroid compound of the formula IA or formula IB as indicated above, or a pharmaceutically acceptable salt thereof,

wherein X_1, X_2, R_1 and R_2 is selected from the group comprising hydrogen, hydroxyl, alkyloxy, oxo and oxyalkyl,

wherein X_3 participates together with X_3' to an oxo functional group, or wherein X_3 is selected from the group comprising hydrogen, hydroxyl, oxyalkyl, oxycarbonyl, and X'_3 is selected from the group comprising alkyl, aryl and aralkyl;

wherein X_4 and X_7 are independently selected from the group comprising hydrogen, oxygen, oxo and hydroxyl;

wherein X_5 and X_6 are hydrogen or wherein X_5 participates to a double bond between the carbon atoms in position 4 and 5, and X_6 is hydrogen, and

wherein n is an integer between 0 and 2.

In an even more preferred embodiment, the present invention relates to a steroid compound of the formula IA or formula IB as indicated above, or a pharmaceutically acceptable salt thereof,

wherein X_1, X_2, X_3, X_3', X_6, X_7, R_1, R_2 and n are selected from the group indicated as above, and

wherein X_4 is equal to X_5 and is selected from the group comprising halogen, aminoalkyl, aminoaryl, optionally substituted by one or more substituents independently selected from the group comprising alkyl, aralkyl, aryl, Het^1, Het^2, cycloalkyl, alkyloxy, alkyloxycarbonyl, carboxyl and aminocarbonyl, or wherein X_5 participates to a double bond between the carbon atoms in position 5 and 6, and X_4 is independently selected from the group comprising hydrogen, aminoalkyl, aminoaryl, optionally substituted by one or more substituents independently selected from the group comprising alkyl, aralkyl, aryl, Het^1, Het^2, cycloalkyl, alkyloxy, alkyloxycarbonyl, carboxyl and aminocarbonyl.

In yet another embodiment, the invention relates to a compound having the formula IA or IB as indicated above, or a pharmaceutically acceptable salt thereof, wherein X_1, X_2, X_3, X_3', X_6, X_7, R_1, R_2 and n are selected from the group indicated in claims 1 to 4; and

wherein X_5 may form with X_6 a single bond when X_5 or X_6 represents an oxygen atom thereby forming an –O- functional group.

Particularly preferred compound according to the invention is a compound having the formula IA as indicated above, or a pharmaceutically acceptable salt thereof, wherein X_1 and X_2 are –OMe, wherein R_1 and R_2 are –H, wherein X_3 is –OH, wherein X_4 is hydrogen, wherein X_5 participates to a double bond between the carbon atoms in position 5 and 6, wherein X_6 is –H, wherein X_7 is hydroxyl and wherein n is 0.

Another particularly preferred compound according to the invention is a compound having the formula IB as indicated above, or a pharmaceutically acceptable salt thereof, wherein X_1 and X_2 are –OMe, wherein R_1 and R_2 are –H, wherein X_4 and X_7 are oxo, wherein X_3 participates together with X_3' to an oxo functional group, wherein X_5 participates to a double bond between the carbon atoms in position 4 and 5, wherein X_6 is hydrogen, and wherein n is 0.

Yet another particularly preferred compound according to the invention is a compound having the formula IA as indicated above, or a pharmaceutically acceptable salt thereof, wherein X_1 and X_2 are –OMe, wherein R_1 and R_2 are –H, wherein X_4 and X_7 are oxo, wherein X_3 is -OH, wherein X_5 participates to a double bond between the carbon atoms in position 4 and 5, wherein X_6 is hydrogen, and wherein n is 0.

The compounds according to the invention show cytotoxic activities, which implies that they may be used in various medical applications. As is demonstrated in the examples provided below, the compounds according to the invention have *in vitro* anti-tumor activity.

Furthermore, the compounds according to the invention exhibit a low toxicity level. The terms "toxicity" or 'toxic effects" as used herein refer to the detrimental effect(s) a compound may have on healthy cells, tissues or organs. The toxicity level of the compounds according to the invention is surprisingly low. The compounds according to the invention combine the essential features of a good anti-tumor activity and a low level of toxicity. Consequently the compounds according to the invention may be used in pharmaceutical compositions for the treatment of various diseases. In addition, because they have a low level of toxicity the compounds according to the invention may be used during longer periods of treatments.

In addition, the compounds according to the invention also have shown an anti-migratory effect. The compounds according to the invention have the ability to stop the migration of

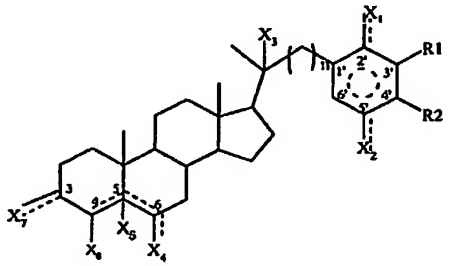
cells away from the neoplastic tumor tissue and thus enable to reduce the colonization of new tissues by these cells.

Method of preparation

In another embodiment, the present invention relates to methods for preparing the compounds according to the invention. Figure 1 represents a scheme of the methods of preparation according to the invention.

Formula IA

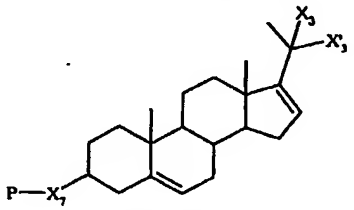
In one embodiment, the invention relates to a method for synthesizing a compound having the structural formula IA,



formula IA

wherein X_1, X_2, X_3, X_4, X_5, X_6, X_7, R_1, R_2 and n are selected from the group as indicated above, said method comprising the steps of

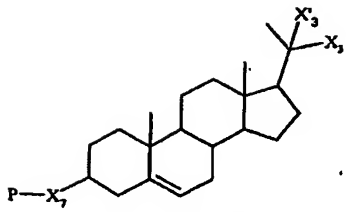
a) providing a starting material having the structural formula IV,



formula IV

wherein X_3, X_3' and X_7 are selected from the group as indicated above, and wherein preferably X_3 participates together with X_3' to an oxo functional group and wherein P is a protecting group selected from the group comprising alkyl aryl silane, alkyl silane, carbonylalkylaryl, and wherein P preferably is t-butyl diphenyl silane,

(b) hydrogenating the compound of step a) thereby obtaining a compound having the structural formula III'A

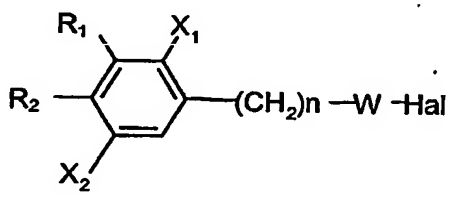


formula III'A

wherein X_3, X_3' and X_7 are selected from the group as indicated above, and wherein X_3 and X_3' preferably form oxo, and

wherein P is a protecting group as indicated above,

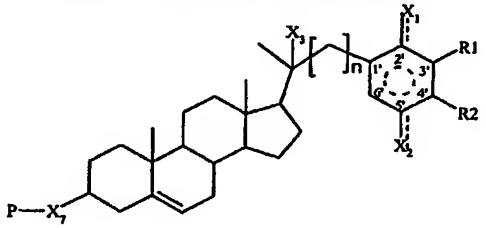
c) effecting reaction between the compound of step b) with an organometallic compound having the structural formula V



formula V

wherein X_1, X_2, R_1, R_2 and n are selected from the group as indicated above, wherein W is a metal or a combination of metals selected from the group comprising magnesium and copper and wherein Hal is a halogen atom, preferably selected from the group comprising bromine, chlorine and iodine,

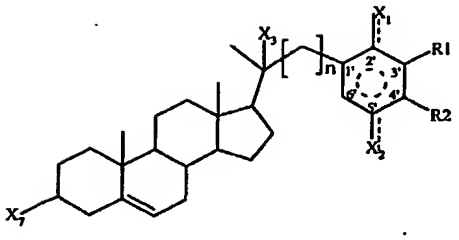
to result in an intermediate having the structural formula IIIA



formula IIIA

wherein X_1, X_2, X_3, X_7, R_1, R_2 and n are selected from the group as indicated above, and wherein P is a protecting group as indicated above,

d) deprotecting the X_7 group of the compound obtained in step c) to form an intermediate having the structural formula IIA



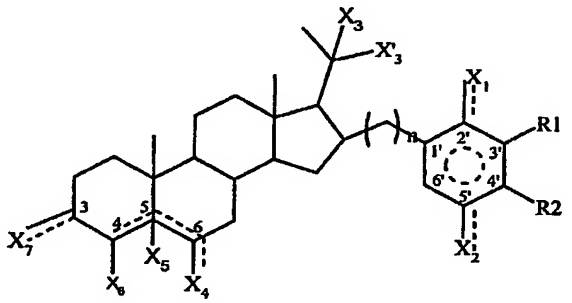
formula II A

wherein X_1, X_2, X_3, X_7, R_1, R_2 and n are selected from the group as indicated above, and

e) oxidizing by reaction with a suitable oxidizing agent or agents to form a compound of formula IA.

Formula IB

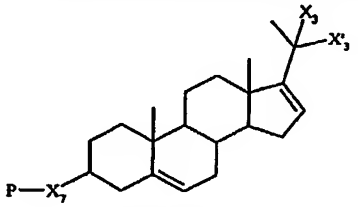
In another embodiment, the invention relates to a method for synthesizing a compound having the structural formula IB



formula IB

wherein X_1, X_2, X_3, X_3', X_4, X_5, X_6, X_7, R_1, R_2 and n are selected from the group as indicated above, said method comprising the steps of

a) providing a starting material having the structural formula IV,

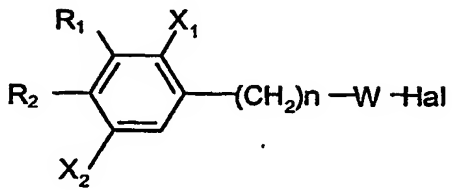


formula IV

wherein X_3, X_3' and X_7 are selected from the group as indicated above, and wherein X_3 and X_3' preferably form oxo, and

wherein P is a protecting group selected from the group comprising alkyl aryl silane, alkyl silane and carbonylalkylaryl, and wherein P preferably is t-butyl diphenyl silane,

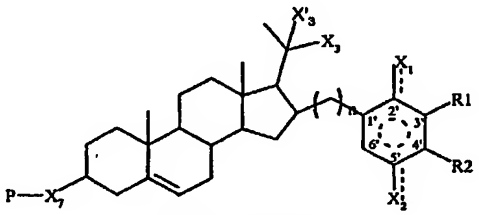
(b) effecting reaction between the compound of step a) with an organometallic compound having the structural formula V



formula V

wherein X_1, X_2, R_1, R_2 and n are selected from the group as indicated above, wherein W is a metal or a combination of metals selected from the group comprising magnesium and copper and wherein Hal is a halogen atom, and preferably selected from the group comprising bromine, chlorine and iodine,

to result in an intermediate having the structural formula III'B



formula III'B

wherein X_1, X_2, X_3, X_3', X_7 R_1, R_2 and n are selected from the group as indicated above, and wherein preferably X_3 participates together with X_3' to an oxo functional group, wherein P is a protecting group as indicated above,

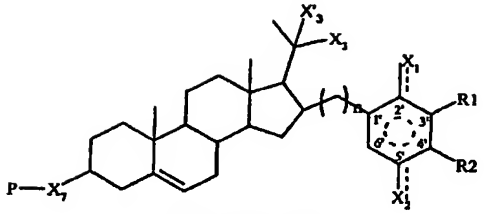
c) effecting reaction between the compound of step b) with an organometallic compound having the structural formula VI

HAL-W-X'_3

formula VI

wherein X'_3 is selected from the group as indicated above, wherein W is a metal or a combination of metals selected from the group comprising magnesium and copper, and wherein Hal is a halogen atom, preferably selected from the group comprising bromine, chlorine and iodine,

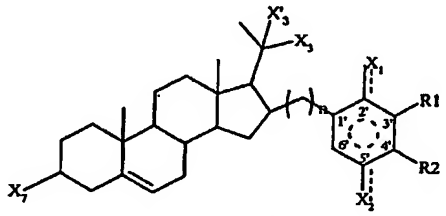
to result in an intermediate having the structural formula IIIB



formula IIIB

wherein X_1, X_2, X_3, X'_3 X_7, R_1, R_2 and n are selected from the group as indicated above, wherein p is a protecting group, and wherein X'3 is selected from the group as indicated above,

d) deprotecting the X_7 group of the compound obtained in step c) to form an compound having the structural formula IIB



formula II B

wherein X_1, X_2, X_3, X'_3, X_7, R_1, R_2 and n are selected from the group as indicated above, and

e) oxidizing by reaction with a suitable oxidizing agent or agents to form a compound of formula IB.

The steroid compounds according to the present invention are prepared using an enone as the starting compound. These enones, having general formula IV, can be synthesised according to the procedure described in Tetrahedron, 1993, 49(23), 5079-5090. The derivatives represented by formula V or formula VI are prepared either from corresponding commercially available halides or by known methods as described for instance in Tetrahedron, 1982, 3555-3561. Example 2 provided below illustrates the preparation of several different steroid compounds according to the invention

In another embodiment, the present invention also relates to a compound, which is obtained by any of the steps according to the above-described methods for synthesis of a compound of formula IA or IB. A number of these compounds identified herein as intermediates also find utility as pharmaceutical agents. Certain intermediate compounds

obtained in any of the above-described steps of the synthesis methods may be useful in the treatment disorders, in particular cancers.

Uses of the compounds according to the invention

An important feature attributed to the compounds according to the invention is their broad application possibility. The compounds according to the invention exhibit anti-tumor activity on a broad panel of histological tumor types. As will be shown in the examples described below, the compounds according to the invention exert significant anti-tumor effects on several tumor models tested, including glioma, colon, lung and bladder cancer (see e.g. example 3).

In addition, the compounds according to the invention also exhibit anti-migratory effect on cancer cells, as illustrated in example 4 provided below.

Due to these interesting properties; in particular the anti-tumor activity, the anti-migratory effect and the low level of toxicity, the steroid compounds according to the invention are particularly suitable for use as a medicament in the treatment of diseases associated with cell proliferation, and even in particular in the treatment of cancer. Therefore, in another embodiment, the invention relates to compounds according to the invention for use as a medicament. In yet another embodiment, the invention provides compounds for use in the preparation of a medicament for treating cancer.

The term "diseases associated with cell proliferation" as used herein refers to, but is not limited to, any type of cancer or condition involving cell proliferation. The compounds of the invention may be especially used in the treatment of cancers such as but not limited to leukemia, non-small cell lung cancer, small cell lung cancer, CNS cancer, melanoma, ovarian cancer, renal cancer, prostate cancer, breast cancer, glioma, colon cancer, bladder cancer, sarcoma, pancreatic cancer, colorectal cancer, head and neck cancer, liver cancer and hematological cancer and lymphoma.

In addition, the compounds according to the invention may also be very suitable in the treatment of scar tissue and wounds. It is believed that most, if not all, of the compounds of the present invention can act as active ingredients in treating scar tissue and in promoting wound healing and tissue regeneration.

Pharmaceutical compositions comprising the steroid compounds

In another embodiment, the present invention relates to a pharmaceutical composition comprising a pharmaceutically acceptable excipient and a therapeutic amount of a compound according to the invention.

The term "therapeutically effective amount" as used herein means that amount of active compound or component or pharmaceutical agent that elicits the biological or medicinal response in a tissue, system, animal or human that is being sought by a researcher, veterinarian, medical doctor or other clinician, which includes alleviation of the symptoms of the disease being treated.

The pharmaceutical composition can be prepared in a manner known per se to one of skill in the art. For this purpose, at least one compound having formula IA or IB, one or more solid or liquid pharmaceutical excipients and, if desired, in combination with other pharmaceutical active compounds, are brought into a suitable administration form or dosage form which can then be used as a pharmaceutical in human medicine or veterinary medicine.

Particular forms of the pharmaceutical composition may be, for example, solutions, suspensions, emulsions, creams, tablets, capsules, nasal sprays, liposomes or micro-reservoirs, especially compositions in orally ingestible or sterile injectable form, for example, as sterile injectable aqueous or oleaginous suspensions or suppositories. The preferred form of composition contemplated is the dry solid form, which includes capsules, granules, tablets, pills, boluses and powders. The solid carrier may comprise one or more excipients, e.g. lactose, fillers, disintegrating agents, binders, e.g. cellulose, carboxymethylcellulose or starch or anti-stick agents, e.g. magnesium stearate, to prevent tablets from adhering to tabletting equipment. Tablets, pills and boluses may be formed so as to disintegrate rapidly or to provide slow release of the active ingredient.

In order to enhance the solubility and/or the stability of the compounds of a pharmaceutical composition according to the invention, it can be advantageous to employ α-, β- or γ-cyclodextrins or their derivatives. In addition, co-solvents such as alcohols may improve the solubility and/or the stability of the compounds. In the preparation of aqueous compositions, addition of salts of the compounds of the invention are obviously more suitable due to their increased water solubility.

[redacted]

Appropriate cyclodextrins are α-, β- or γ-cyclodextrins (CDs) or ethers and mixed ethers thereof wherein one or more of the hydroxy groups of the anhydroglucose units of the cyclodextrin are substituted with alkyl, particularly methyl, ethyl or isopropyl, e.g. randomly methylated β-CD; hydroxyalkyl, particularly hydroxyethyl, hydroxypropyl or hydroxybutyl; carboxyalkyl, particularly carboxymethyl or carboxyethyl; alkylcarbonyl, particularly acetyl; alkyloxycarbonylalkyl or carboxyalkyloxyalkyl, particularly carboxymethoxypropyl or carboxyethoxypropyl; alkylcarbonyloxyalkyl, particularly 2-acetyloxypropyl. Especially noteworthy as complexants and/or solubilizers are β-CD, randomly methylated β-CD, 2,6-dimethyl- β-CD, 2-hydroxyethyl-β-CD, 2-hydroxyethyl-γ-CD, 2-hydroxypropyl-γ-CD and (2-carboxymethoxy)propyl- β-CD, and in particular 2-hydroxypropyl- β-CD (2-HP- β-CD). The term mixed ether denotes cyclodextrin derivatives wherein at least two cyclodextrin hydroxy groups are etherified with different groups such as, for example, hydroxypropyl and hydroxyethyl. An interesting way of formulating the analogues in combination with a cyclodextrin or a derivative thereof has been described in EP-A-721,331. Although the formulations described therein are with antifungal active ingredients, they are equally interesting for formulating the analogues. Said formulations may also be rendered more palatable by adding pharmaceutically acceptable sweeteners and/or flavors.

More in particular, the compositions may be formulated in a pharmaceutical formulation comprising a therapeutically effective amount of particles consisting of a solid dispersion of the compounds of the invention and one or more pharmaceutically acceptable water-soluble polymers.

The term "a solid dispersion" defines a system in a solid state (as opposed to a liquid or gaseous state) comprising at least two components, wherein one component is dispersed more or less evenly throughout the other component or components. When said dispersion of the components is such that the system is chemically and physically uniform or homogenous throughout or consists of one phase as defined in thermodynamics, such a solid dispersion is referred to as "a solid solution". Solid solutions are preferred physical systems because the components therein are usually readily bioavailable to the organisms to which they are administered. The term "a solid dispersion" also comprises dispersions that are less homogenous throughout than solid solutions. Such dispersions are not chemically and physically uniform throughout or comprise more than one phase.

The water-soluble polymer is conveniently a polymer that has an apparent viscosity of 1 to 100 mPa.s when dissolved in a 2 % aqueous solution at 20°C solution. Preferred water-soluble polymers are hydroxypropyl methylcelluloses or HPMC. HPMC having a methoxy

degree of substitution from about 0.8 to about 2.5 and a hydroxypropyl molar substitution from about 0.05 to about 3.0 are generally water soluble. Methoxy degree of substitution refers to the average number of methyl ether groups present per anhydroglucose unit of the cellulose molecule. Hydroxy-propyl molar substitution refers to the average number of moles of propylene oxide which have reacted with each anhydroglucose unit of the cellulose molecule. The uscharin analogues as defined hereinabove can be prepared by first preparing a solid dispersion of the uscharin analogues, and then optionally grinding or milling that dispersion. Various techniques exist for preparing solid dispersions including melt-extrusion, spray-drying and solution-evaporation, melt-extrusion being preferred.

It may further be convenient to formulate the analogues in the form of nanoparticles which have a surface modifier adsorbed on the surface thereof in an amount sufficient to maintain an effective average particle size of less than 1000 nm. Suitable surface modifiers can preferably be selected from known organic and inorganic pharmaceutical excipients. Such excipients include various polymers, low molecular weight oligomers, natural products and surfactants. Preferred surface modifiers include nonionic and anionic surfactants.

Yet another interesting way of formulating the compounds according to the invention involves a pharmaceutical composition whereby the compounds are incorporated in hydrophilic polymers and applying this mixture as a coat film over many small beads, thus yielding a composition with good bio-availability which can conveniently be manufactured and which is suitable for preparing pharmaceutical dosage forms for oral administration. Said beads comprise (a) a central, rounded or spherical core, (b) a coating film of a hydrophilic polymer and an antiretroviral agent and (c) a seal-coating polymer layer. Materials suitable for use as cores in the beads are manifold, provided that said materials are pharmaceutically acceptable and have appropriate dimensions and firmness. Examples of such materials are polymers, inorganic substances, organic substances, and saccharides and derivatives thereof.

Methods of treatment

As indicated above, due to their favourable anti-tumor properties of the compounds according to the present invention are particularly useful in the treatment of individuals suffering from cancer. Therefore, in another embodiment, the present invention also relates to the use of the steroid compounds according to the invention or to a pharmaceutical composition comprising said steroid compounds in the treatment of cancer. A method of treating cancer comprises administering to an individual in need of

such treatment a pharmaceutical composition comprising the steroid compounds according to the invention.

For these purposes, the pharmaceutical composition of the present invention may be administered orally, parenterally, i.e. including subcutaneous injections, intravenous, intramuscular, intrasternal injection or infusion techniques, by inhalation spray, or rectally, in dosage unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles.

In accordance with the method of the present invention, said pharmaceutical composition can be administered separately at different times during the course of therapy or concurrently in divided or single combination forms. The present invention is therefore to be understood as embracing all such regimes of simultaneous or alternating treatment and the term "administering" is to be interpreted accordingly.

Essentially, the primary modes of treatment of solid tumor cancers comprise surgery, radiation therapy and chemotherapy, separately and in combination. The compounds according to the invention are suitable for use in combination with these medicinal techniques. The compounds of the invention may be useful in increasing the sensitivity of tumor cells to radiation in radiotherapy and also in potentiating or enhancing damage to tumors by chemotherapeutic agents. The compounds and their pharmaceutically acceptable salts may also be useful for sensitising multidrug-resistant tumor cells. The compounds according to the invention are useful therapeutic compounds for administration in conjunction with other DNA-damaging cytotoxic drugs or radiation used in radiotherapy to potentiate their effect.

In another embodiment of the method of the invention, the administration may be performed with food, e.g., a high-fat meal. The term 'with food' means the consumption of a meal either during or no more than about one hour before or after administration of a pharmaceutical composition according to the invention.

For an oral administration form, the compositions of the present invention can be mixed with suitable additives, such as excipients, stabilizers or inert diluents, and brought by means of the customary methods into the suitable administration forms, such as tablets, coated tablets, hard capsules, aqueous, alcoholic, or oily solutions. Examples of suitable inert carriers are gum arabic, magnesia, magnesium carbonate, potassium phosphate, lactose, glucose, or starch, in particular, corn starch. In this case, the preparation can be

carried out both as dry and as moist granules. Suitable oily excipients or solvents are vegetable or animal oils, such as sunflower oil or cod liver oil. Suitable solvents for aqueous or alcoholic solutions are water, ethanol, sugar solutions, or mixtures thereof. Polyethylene glycols and polypropylene glycols are also useful as further auxiliaries for other administration forms. As immediate release tablets, these compositions may contain microcrystalline cellulose, dicalcium phosphate, starch, magnesium stearate and lactose and/or other excipients, binders, extenders, disintegrants, diluents and lubricants known in the art.

The oral administration of a pharmaceutical composition comprising a steroid compound according to the invention, or a pharmaceutically acceptable salt or ester thereof, is suitably accomplished by uniformly and intimately blending together a suitable amount of the steroid compound in the form of a powder, optionally also including a finely divided solid carrier, and encapsulating the blend in, for example, a hard gelatin capsule. The solid carrier can include one or more substances, which act as binders, lubricants, disintegrating agents, coloring agents, and the like. Suitable solid carriers include, for example, calcium phosphate, magnesium stearate, talc, sugars, lactose, dextrin, starch, gelatin, cellulose, polyvinylpyrrolidine, low melting waxes and ion exchange resins.

Oral administration of a pharmaceutical composition comprising an steroid compound according to the invention, or a pharmaceutically acceptable salt or ester thereof can also be accomplished by preparing capsules or tablets containing the desired amount of the steroid compound, optionally blended with a solid carrier as described above. Compressed tablets containing the pharmaceutical composition of the invention can be prepared by uniformly and intimately mixing the active ingredient with a solid carrier such as described above to provide a mixture having the necessary compression properties, and then compacting the mixture in a suitable machine to the shape and size desired. Molded tablets maybe made by molding in a suitable machine, a mixture of powdered steroid compound moistened with an inert liquid diluent.

When administered by nasal aerosol or inhalation, these compositions may be prepared according to techniques well-known in the art of pharmaceutical formulation and may be prepared as solutions in saline, employing benzyl alcohol or other suitable preservatives, absorption promoters to enhance bioavailability, fluorocarbons, and/or other solubilizing or dispersing agents known in the art. Suitable pharmaceutical formulations for administration in the form of aerosols or sprays are, for example, solutions, suspensions or emulsions of the compounds of the invention or their physiologically tolerable salts in a

pharmaceutically acceptable solvent, such as ethanol or water, or a mixture of such solvents. If required, the formulation can also additionally contain other pharmaceutical auxiliaries such as surfactants, emulsifiers and stabilizers as well as a propellant.

For subcutaneous or intravenous administration, the active analogue, if desired with the substances customary therefor such as solubilizers, emulsifiers or further auxiliaries, are brought into solution, suspension, or emulsion. The compounds of the invention can also be lyophilized and the lyophilizates obtained used, for example, for the production of injection or infusion preparations. Suitable solvents are, for example, water, physiological saline solution or alcohols, e.g. ethanol, propanol, glycerol, in addition also sugar solutions such as glucose or mannitol solutions, or alternatively mixtures of the various solvents mentioned. The injectable solutions or suspensions may be formulated according to known art, using suitable non-toxic, parenterally-acceptable diluents or solvents, such as mannitol, 1,3-butanediol, water, Ringer's solution or isotonic sodium chloride solution, or suitable dispersing or wetting and suspending agents, such as sterile, bland, fixed oils, including synthetic mono- or diglycerides, and fatty acids, including oleic acid.

When rectally administered in the form of suppositories, these formulations may be prepared by mixing the compounds according to the invention with a suitable non-irritating excipient, such as cocoa butter, synthetic glyceride esters or polyethylene glycols, which are solid at ordinary temperatures, but liquidify and/or dissolve in the rectal cavity to release the drug.

The pharmaceutical compositions of this invention can be administered to humans in dosage ranges specific for each analogue comprised in said compositions. The compounds comprised in said composition can be administered together or separately.

It will be understood, however, that specific dose level and frequency of dosage for any particular patient may be varied and will depend upon a variety of factors including the activity of the specific analogue employed, the metabolic stability and length of action of that compound, the age, body weight, general health, sex, diet, mode and time of administration, rate of excretion, drug combination, the severity of the particular condition, and the host undergoing therapy.

The following examples are meant to illustrate the present invention. These examples are presented to exemplify the invention and are not to be considered as limiting the scope of the invention. Example 1 provides a non-limiting list of examples of compounds according

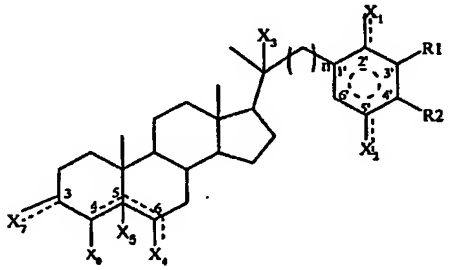
to the invention. Example 2 illustrates the preparation of different compounds according to the invention. Example 3 illustrates *in vitro* anti-tumor effects of several compounds according to the invention.

Examples

The practice of the present invention will employ, unless otherwise indicated, conventional techniques of synthetic organic chemistry, biological testing, and the like, which are within the skill of the art. Such techniques are explained fully in the literature.

Example 1 *Non-limiting examples of compounds according to the invention having general formula IA or general formula IB are listed hereunder in Table A or Table B, respectively*

Formula IA



Formula IB

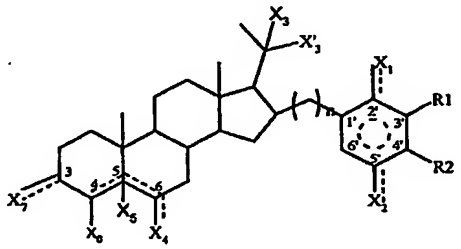
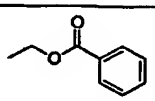
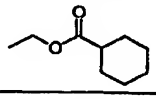
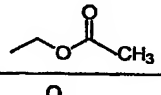
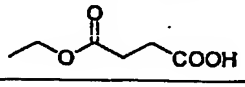
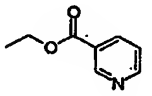
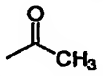
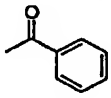
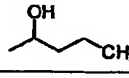
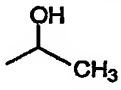
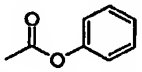
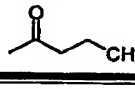


Table A

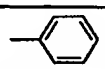
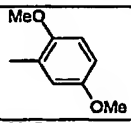
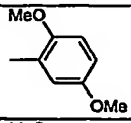
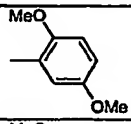
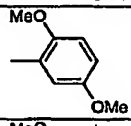
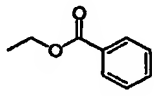
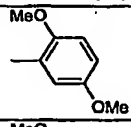
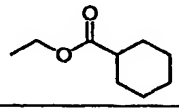
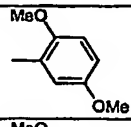
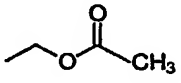
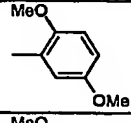
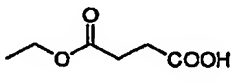
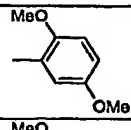
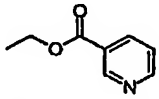
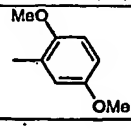
X_1	X_2	X_3	X_4	X_5	X_6	X_7	R_1	R_2	n
-O-CH_3	-O-CH_3	-OH	=O	-*	-H	=O	-H	-H	0
-CH_3	-O-CH_3	-OH	=O	-*	-H	=O	-H	-H	0
-COOH	-O-CH_3	-OH	=O	-*	-H	=O	-H	-H	0
-CH=CH_2	-O-CH_3	-OH	=O	-*	-H	=O	-H	-H	0
-O-CH_3	-O-CH_3	-OH	=O	-*	-H	=O	-H	-H	1
-CO_2CH_3	=O	-OH	=O	-*	-H	=O	-H	-H	1
-$CO_2C_2H_5$	=O	-OH	=O	-*	-H	=O	-H	-H	1
-CHO	=O	-OH	=O	-*	-H	=O	-H	-H	1
-CH_2OH	=O	-OH	=O	-*	-H	=O	-H	-H	1
-$CHOHCH_3$	=O	-OH	=O	-*	-H	=O	-H	-H	1
-CH_2-CH_2-CH=CH_2	-COOH	-OH	=O	-*	-H	=O	-H	-H	1

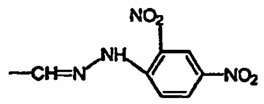
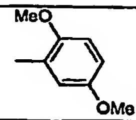
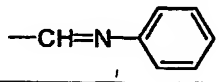
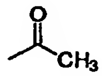
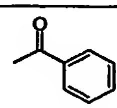
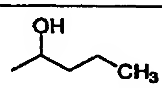
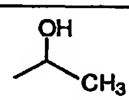
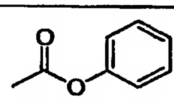
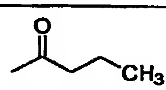
$-COOCH_3$	-COOH	-OH	=0	-*	-H	=0	-H	-H	1
$-CH_2OCH_3$	-COOH	-OH	=0	-*	-H	=0	-H	-H	1
$-CH_2OCH_2CH_3$	-COOH	-OH	=0	-*	-H	=0	-H	-H	1
$-CH_2SCH_3$	-COOH	-OH	=0	-*	-H	=0	-H	-H	1
	$-CH_3$	-OH	=0	-*	-H	=0	-H	-H	1
	$-CH_3$	-OH	=0	-*	-H	=0	-H	-H	2
	$-CH_3$	-OH	=0	-*	-H	=0	-H	-H	2
	$-CH_3$	-OH	=0	-*	-H	=0	-H	-H	2
	$-CH=CH_2$	-OH	=0	-*	-H	=0	-H	-H	2
	$-CH=CH_2$	-OH	=0	-*	-H	=0	-H	-H	3
	$-CH=CH_2$	-OH	=0	-*	-H	=0	-H	-H	3
	$-CH_2SCH_3$	-OH	=0	-*	-H	=0	-H	-H	3
	$-CH_2SCH_3$	-OH	=0	-*	-H	=0	-H	-H	3
	$-CH_2SCH_3$	-OH	=0	-*	-H	=0	-H	-H	3
	$-CH_2SCH_3$	-OH	=0	-*	-H	=0	-H	-H	3

* refers to fact that X_5 participates to a double bond between the carbon atoms in position 4 and 5

TABLE B

X_1	X_2	X_3	X_3'	X_4	X_5	X_6	X_7	R_1	R_2	n
$-O-CH_3$	=0	-OH	$-(CH_2)-CH-(CH3)_2$	=0	-*	-H	=0	-H	-H	0
$-O-CH_3$	$-CH_3$	-OH	$-(CH_2)-CH-(CH3)_2$	=0	-*	-H	=0	-H	-H	0

-O-CH_3	-COOH	-OH	-(CH_2)-CH-$(CH3)_2$	=0	-*	-H	=0	-H	-H	0
-O-CH_3	-CH=CH_2	-OH	-(CH_2)-CH-$(CH3)_2$	=0	-*	-H	=0	-H	-H	0
-O-CH_3	-O-CH_3	-OH	-(CH_2)-CH-$(CH3)_2$	=0	-*	-H	=0	-H	-H	0
=O	-CO_2CH_3	-OH	-(CH_2)-CH-$(CH3)_2$	=0	-*	-H	=0	-H	-H	0
=O	-$CO_2C_2H_5$	-OH	-(CH_2)-CH-$(CH3)_2$	=0	-*	-H	=0	-H	-H	0
=O	-CHO	-OH		=0	-*	-H	=0	-H	-H	0
=O	-CH_2OH	-OH		=0	-*	-H	=0	-H	-H	1
=O	-$CHOHCH_3$	-OH		=0	-*	-H	=0	-H	-H	1
-COOH	-CH_2-CH_2-CH=CH_2	-OH		=0	-*	-H	=0	-H	-H	1
-COOH	-$COOCH_3$	-OH		=0	-*	-H	=0	-H	-H	1
-COOH	-CH_2OCH_3	-OH		=0	-*	-H	=0	-H	-H	1
-COOH	-$CH_2OCH_2CH_3$	-OH		=0	-*	-H	=0	-H	-H	1
-COOH	-CH_2SCH_3	-OH		=0	-*	-H	=0	-H	-H	1
-CH_3	-CH=N-OH	-OH		=0	-*	-H	=0	-H	-H	1
-CH_3		-OH		=0	-*	-H	=0	-H	-H	1
-CH_3		-OH		=0	-*	-H	=0	-H	-H	2
-CH_3		-OH		=0	-*	-H	=0	-H	-H	2
-CH_3		-OH		=0	-*	-H	=0	-H	-H	2
-$CH=CH_2$		-OH		=0	-*	-H	=0	-H	-H	2

-CH=CH$_2$		-OH		=0	-*	-H	=0	-H	-H	2
-CH=CH$_2$		-OH	-(CH$_2$)-CH-(CH3)$_2$	=0	-*	-H	=0	-H	-H	2
-CH=CH$_2$		-OH	-(CH$_2$)-CH-(CH3)$_2$	=0	-*	-H	=0	-H	-H	2
-CH=CH$_2$		-OH	-(CH$_2$)-CH-(CH3)$_2$	=0	-*	-H	=0	-H	-H	3
-CH$_2$SCH$_3$		-OH	-(CH$_2$)-CH-(CH3)$_2$	=0	-*	-H	=0	-H	-H	3
-CH$_2$SCH$_3$		-OH	-(CH$_2$)-CH-(CH3)$_2$	=0	-*	-H	=0	-H	-H	3
-CH$_2$SCH$_3$		-OH	-(CH$_2$)-CH-(CH3)$_2$	=0	-*	-H	=0	-H	-H	3
-CH$_2$SCH$_3$		-OH	-(CH$_2$)-CH-(CH3)$_2$	=0	-*	-H	=0	-H	-H	3

* refers to fact that X_5 participates to a double bond between the carbon atoms in position 4 and 5

Example 2 Preparation of steroid compounds according to the invention

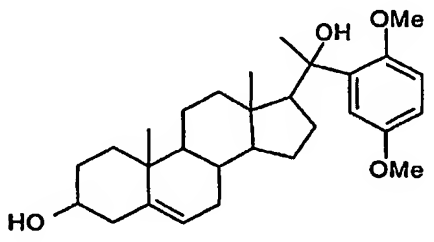
The present example provides evidence for the preparation of three different compounds according to the invention, **UBS1740, UBS1664** and **UBS1819.** The prepared compounds and their intermediates are represented in Table C. In addition, this example also illustrates the preparation of a reference compound, UBS 881. The compounds and their intermediate products are schematically represented in Table C.

1. Preparation of compound UBS1740

UBS1697 was prepared by hydrogenating the compound having formula IV (100mg, 1.81 10^{-4}mole) in 10ml of ethyl acetate (100mg of 10% Pd/C, H_2 at 45psi) for 24 hours. The palladium was filtered and the solvent was evaporated under reduced pressure. The obtained product, indicated with formula III'$_{A1}$ in fig. 1, was purified by flash chromatography on silica gel (hexane/acetone 95/5) to give 77mg of compound **UBS1697.** The yield of this preparation process was 77%.

A solution of 2,5-dimethoxybenzene (391mg, 1.80 10^{-3}mole) and 1,2-dibromo-ethane (337mg, 1.79 10^{-3}mole) in dry tetrahydrofuran (2ml) was added dropwise over 15min to a stirred mixture of Mg (200mg, 8.23 10^{-3}mole) and I_2 (trace amount) in dry tetrahydrofuran (2ml) under N_2. After the addition, a solution of the compound UBS 1697 (100mg, 1.90 10^{-4} mole) in dry tetrahydrofuran (1ml) was added dropwise over 5min. After 15min, a saturated NH_4Cl solution was added and the mixture was extracted with ether. The ether solution was washed with brine, dried ($MgSO_4$), filtered and concentrated in vacuo. The residue was chromatographed over silica gel (hexane/acetone 95/5) in order to provide 84mg of compound **UBS1717**. The yield of this preparation process was 67%.

Subsequently, a 1M solution of n-Bu4NF (200µl, 2 10^{-4} mole) was added to a solution of the compound III_{A1} (UBS 1717) (50mg, 7.21 10^{-5} mole) in tetrahydrofuran (5ml) and the mixture was stirred for 3 days at room temperature. Purification of the crude mixture by silica gel flash chromatography (hexane/AcOEt 3/1) provided 25mg of the compound **UBS1740**. The yield of this preparation process was 76%.



UBS1740

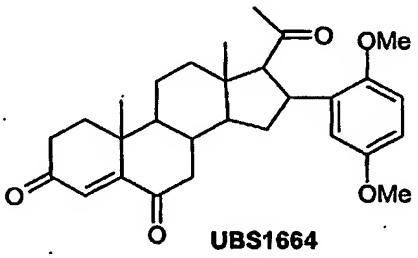
2. Preparation of compound UBS1664

In a similar manner as described for the preparation of UBS 1717, the compound of formula IV (200mg, 3.62 10^{-4} mole) was treated with 2,5-dimethoxybenzene (314mg, 1.60 10^{-3}mole) and magnesium (150mg, 5.78 10^{-3} mole) to obtain 60mg of the compound **UBS1513**. The yield of this preparation process was 24%.

In a similar manner as described as described for the preparation of UBS 1740, the compound UBS 1513 (150mg, 2.17 10-4 mole) was treated with a solution 1M of *n*-Bu_4NF (650µl, 6.52 10^{-4} mole) in tetrahydrofuran to give 700mg of compound **UBS1634**. The yield of this process was 70%.

PCC (238mg, 1.1 10^{-3} mole) was added in one portion to a solution of steroid II_{B1} (100mg, 2.20 10^{-4} mole) in dry CH_2Cl_2 (10ml) for 48h.. Subsequent addition of Et_2O and filtration provided an organic solution, which was washed with water, dried, filtered and evaporated

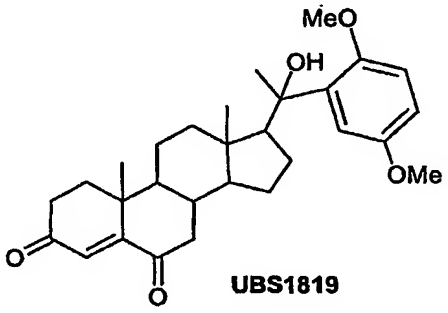
to give crude product. Purification of this crude mixture by silica gel chromatography (hexane/AcOEt 1/2) provided pure compound **UBS1664**. The yield of this process was 61%.



UBS1664

3. Preparation of compound UBS 1819

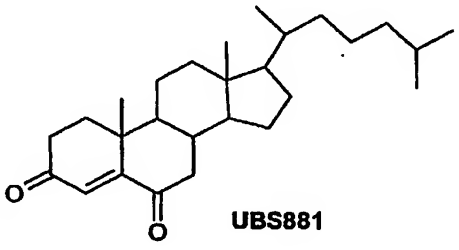
The compound UBS1819 was obtained starting from **UBS1740**. In a similar manner as described for the preparation of UBS 1664, UBS1740 (50mg, 1.10 10^{-4} mole) was treated with PCC (52mg, 2.42 10^{-4} mole) and calcium carbonate (220mg, 2.20 10^{-3} mole) to obtain compound **UBS1819**.



UBS1819

4. Preparation of compound UBS 881

The compound UBS881 was obtained starting from cholesterol. In a similar manner as described for the preparation of UBS 1664, cholesterol (400mg, 1.03 10^{-3} mole) was treated with PCC (1.550g, 7.21 10^{-3} mole) to obtain compound **UBS881**. This product is known to be isolated from *Cinachyrella voeltzkowi*, and shows an anti-cancer activity. It was used as reference compound in the below-described experiments



UBS881

Table C Compounds and their intermediates according to the invention

	P	X_1	X_2	X_3	X_3'	X_4	X_5	X_6	X_7	R_1	R_2	n
UBS1697	$tBuPh_2Si$	-	-	=O		-H	-**	-H	-O-	H	H	0
UBS1717	$tBuPh_2Si$	-OMe	-OMe	-OH	-	-H	-**	-H	-O-	H	H	0
UBS1740	-	-OMe	-OMe	-OH	-	-H	-**	-H	-OH	H	H	0
UBS1819	-	-OMe	-OMe	-OH	-	=O	-*	-H	=O	H	H	0
UBS1513	$tBuPh_2Si$	-OMe	-OMe	=O		-H	-**	-H	-O-	H	H	0
UBS1634	-	-OMe	-OMe	=O		-H	-**	-H	-OH	H	H	0
UBS1664	-	-OMe	-OMe	=O		=O	-*	-H	=O	H	H	0

* refers to fact that X_5 participates to a double bond between the carbon atoms in position 4 and 5

** refers to fact that X_5 participates to a double bond between the carbon atoms in position 5 and 6

Example 3 Effect of different compounds according to the invention on overall cell growth of a cell line

In order to characterize the *in vitro* activities of the compounds according to the invention, MTT tests were carried out. The MTT test, which is a well-known test in the art, is an indirect technique that rapidly measures, i.e. within 5 days, the effect of a given product on the overall cell growth. This test measures the number of metabolically active living cells that are able to transform the MTT product (3-(4,5-dimethylthiazol-2-yl)-2,5 diphenyl tetrazolium bromide), having a yellowish color, to the blue product formazan dye by mitochondrial reduction. The amount of formazan obtained at the end of the experiment is measured with a spectrophotometer and is directly proportional to the number of living cells. Determination of the optical density enables a quantitative measurement of the effect of the investigated compounds as compared to the control condition (untreated cells) and to compare it to other reference compound. In the following examples different compounds according to the invention were tested and compared to the reference compound being UBS881.

Six human cancer cell lines, described in Table D, were tested in the presence of the extract according to the invention. These cell lines represent four histological cancer types, being glioma cancer (cell line Hs683 and U-373 MG), colon cancer (cell lineHCT-15 and LoVo), lung cancer (cell line A549) and bladder cancer (cell line J82). The cells were allowed to grow in 96-well micro wells with a flat bottom with an amount of 100 µl of cell

suspension per well to have 1000 to 5000 cells/well depending on cell type. Each cell line was seeded in its own cell culture medium (Table D).

TABLE D Human cancer cell lines and corresponding cell culture medium used for the MTT experiments

Cell lines	ATCC code	Tissue	Medium	Literature Ref.
Hs683	HTB-138	Glioma	MEM 5% serum	J. Natl. Cancer Inst. *56:* 843-849, 1976; *ibid. 58:* 1455-1463, 1977
U-373 MG	HTB-17	Glioma	MEM 5% serum	Acta Pathol. Microbial. Scand. *74:* 465-486, 1968
HCT-15	CCL-225	Colon	MEM 5% serum	Cancer Res. *39:* 1020-1025, 1979
LoVo	CCL-229	Colon	MEM 5% serum	Exp. Cell Res. *101:* 414-416, 1976; J. Natl. Cancer Inst. *61:* 75-83, 1978; Cancer Res. *39:* 2630-2636, 1979
A549	CCL-185	Lung	MEM 5% serum	J. Natl. Cancer Inst. *51:* 1417-1423, 1973; Int. J. Cancer *17:* 62-70, 1976
J82	HTB-1	Bladder	MEM 5% serum	Br. J. Cancer *38:* 64-76, 1978; In Vitro models for cancer research Vol iV. CRC Press, 103-125, 1986

After a 24-hour period of incubation at 37°C, the culture medium is replaced by 100 µl of fresh medium in which the compound to be tested has been dissolved at different required concentrations. Different compounds were tested at 10^{-7} M, $5X10^{-7}$ M, 10^{-6} M, $5X10^{-6}$ M, 10^{-5} M, $5X10^{-5}$ M, 10^{-4} M, $5X10^{-4}$ M, and 10^{-3} M. Each experimental condition was carried out in hexaplicate. The compounds tested were UBS 1664, UBS 1740, and UBS1819. As a reference, UBS881 was used.

After 72 hours of incubation at 37°C with the compound (experimental conditions) or without the compound (control condition), the medium was replaced by 100 µl MTT at the concentration of 1 mg/ml dissolved in RPMI. The micro wells were subsequently incubated during 3 hours at 37° C and centrifuged at 400g during 10 minutes. The MTT was removed and formazan crystals formed, were dissolved in 100 µl DMSO. The micro wells were shaken for 5 minutes and read on a spectrophotometer at the wavelengths of 570 nm corresponding to the maximum formazan absorbance wavelength, and of 630 nm, which is the background noise wavelength.

For each experimental condition, the mean OD associated with the SEM (standard error of the mean) for each condition (6 wells) was calculated. The percentage of remaining living

cells in comparison with the control was calculated. Results of these experiments are represented in figures 2 to 5.

Figure 2 represents the cytotoxic activity of the UBS881 on the 6 tested cancer cell lines. In **figure 3** it is shown that the compound UBS1664 induced cytotoxic activity on all 6 tested cell lines. The cytotoxic activity was stronger on HCT-15, LoVo and A549 lines than on Hs683, U-373MG and J82 cell lines. **Figure 4** represents the cytotoxic activity of UBS1740 on the 6 tested cancer cell lines. The Hs683 and A549 cell lines were most sensitive compared to the other cell lines to UBS1740. **Figure 5** represents the cytotoxic activity of UBS1819 on the 6 tested cell lines. The activities are comparable for each cell line with a IC_{50} value ranged between 5.10^{-5} M to 10^{-5} M. Thus, as illustrated on figures 2 to 5 the compounds according to the invention exerted an anti-tumor activity on different types of cancer cell lines.

The concentration at which the compounds according to the invention kill 50% of cell population, i.e. the IC_{50} value, is represented in table E.

TABLE E Comparison of the IC_{50} value of compounds according to the invention

compound	Hs683	U-373	HCT-15	LoVo	A549	J82
UBS881	10^{-5}, 5.10^{-6}	10^{-5}, 5.10^{-6}	10^{-5}, 5.10^{-6}	10^{-5}, 5.10^{-6}	10^{-5}, 5.10^{-6}	5.10^{-5}, 10^{-5}
UBS1664	10^{-4}, 5.10^{-5}	10^{-4}, 5.10^{-5}	5.10^{-5}, 10^{-5}	5.10^{-5}, 10^{-5}	5.10^{-5}, 10^{-5}	10^{-4}, 5.10^{-5}
UBS1740	10^{-5}, 5.10^{-6}	5.10^{-5}, 10^{-5}	5.10^{-5}, 10^{-5}	5.10^{-5}, 10^{-5}	10^{-5}, 5.10^{-6}	5.10^{-5}, 10^{-5}
UBS1819	5.10^{-5},10^{-5}	5.10^{-5},10^{-5}	5.10^{-5},10^{-5}	5.10^{-5},10^{-5}	5.10^{-5},10^{-5}	5.10^{-5},10^{-5}

Figure 6 compares the cytotoxic activity of UBS1664, UBS1740, UBS1819 to UBS881 on 6 different cancer cell lines. All compounds induced an anti-tumor effect on each tested cell line. The IC_{50} values for UBS 881, UBS 1664, UBS 1740 and UBS 1819 respectively ranged between [5.10^{-5}, 5.10^{-6}], [10^{-4}, 10^{-5}], [5.10^{-5}, 5.10^{-6}] and [5.10^{-5}, 10^{-5}].

In conclusion, the novel compounds according to the invention tested exhibited an anti-tumor effect on the 6 human cancer cell lines assayed in the present experiments. These anti-tumor effects corresponded to marked decreases in the overall growth of these human cancers models belonging to four representative histological types.

Example 4 Effect of a compound according to the invention on cell migration

The present invention illustrates the effect of the compound UBS1664 according to the invention on the migration of cancer cells.

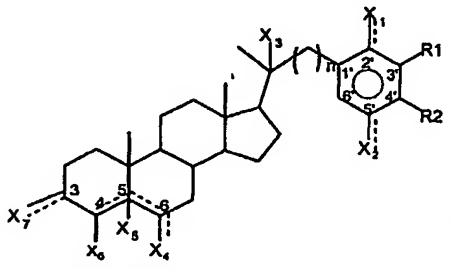
Cells of two different cancer lines, i.e. U-373 MG (Glioma cancer) and A549 (lung cancer) were seeded on culture flask 48 hours before the migration experiment. On the test day, cells were treated with or without compounds UBS881 and UBS1664 in closed Falcon dishes containing a buffered medium at a controlled temperature (37.0 ± 0.1°C) for 12 or 24 hours. The compounds were administered at two non-cytotoxic concentrations (10^{-6} M and 10^{-7} M). Migration of the cells was observed by means of a CCD-camera mounted on a phase-contrast microscope. A statistical analyse of the migration, with the non-parametric Mann-Whitney test, was established for 25% of the most motile cells and for the entire cell population. The table F below illustrates the anti-migratory effect of the compound according to the invention.

Table F Anti-migratory effect of the compound UBS 1664 on cells of two cancer cell lines

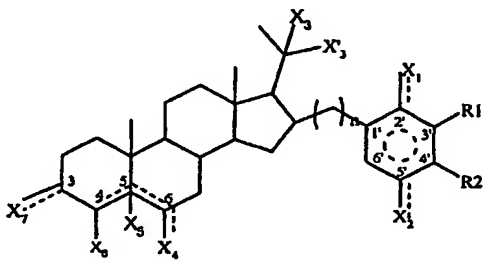
Compounds	Cell lines	Max. effects	Conditions
UBS 881	U-373 MG	-24% / $p < 0,001$	For 24 hours on the 25% of most motile cells, at 10^{-7} M
UBS1664	U-373 MG	-27% / $p < 0,001$	For 24 hours on the 25% of most motile cells, at 10^{-7} M
	A549	-15% / $p < 0,05$	For 12 hours on the entire cell population, at 10^{-7} M

In conclusion, the compounds UBS881 and UBS1664 induced a decrease in the migration level of U-373 MG and A549 cancer cells at the weakest studied concentration, i.e. 10^{-7} M.

In an embodiment, the present invention relates to a compound having the structural formula IA or IB or a pharmaceutically acceptable salt thereof,



formula IA



formula IB

wherein X_1, X_2, R_1 and R_2 are independently selected from the group comprising oxo, hydrogen, hydroxyl, oxyalkyl, alkyl, alkenyl, alkynyl, alkyloxy, alkyloxyalkyl, alkylthioalkyl, alkoxycarbonyl, alkylthiocarbonyl, alkanoyl, cycloalkylalkyl, cycloalkylcarbonyl, cycloalkylalkanoyl, cycloalkylthiocarbonyl, cycloalkylalkoxycarbonyl, cycloalkylalkoxythiocarbonyl, cycloalkylthioalkyl, alkylcarbonyloxyalkyl, cycloalkylcarbonyloxyalkyl, silyloxyalkyl, aralkyl, arylalkenyl, arylcarbonyl, aryloxycarbonyl, arylthiocarbonyl, aralkoxycarbonyl, arylalkylthiocarbonyl, aryloxyalky, arylthioalkyl, haloalkyl, hydroxyalkyl, aralkanoyl, aroyl, aryloxycarbonylalkyl, aryloxyalkanoyl, carboxyl, alkenylcarbonyl, alkynylcarbonyl, Het^1, Het^1alkyl, Het^1oxyalkyl, Het^1aryl, Het^1aralkyl, Het^1cycloalkyl, Het^1alkoxycarbonyl, Het^1alkylthiocarbonyl, Het^1oxycarbonyl, Het^1thiocarbonyl, Het^1alkanoyl, Het^1aralkanoyl, Het^1aryloxyalkyl, Het^1alkyloxyalkyl, Het^1arylthioalkyl, Het^1aryloxycarbonyl, Het^1aralkoxycarbonyl, Het^1aroyl, Het^1oxyalkylcarbonyl, Het^1alkyloxyalkylcarbonyl, Het^1aryloxyalkylcarbonyl, Het^1carbonyloxyalkyl, Het^1alkylcarbonyloxyalkyl, Het^1aralkylcarbonyloxyalkyl, Het^2alkyl, Het^2oxyalkyl, Het^2alkyloxyalkyl, Het^2aralkyl, Het^2carbonyl, Het^2oxycarbonyl, Het^2thiocarbonyl, Het^2alkanoyl, Het^2alkylthiocarbonyl, Het^2alkoxycarbonyl, Het^2aralkanoyl, Het^2aralkoxycarbonyl, Het^2aryloxycarbonyl, Het^2aroyl, Het^2aryloxyalkyl, Het^2arylthioalkyl, Het^2oxyalkylcarbonyl, Het^2alkyloxyalkylcarbonyl, Het^2aryloxyalkylcarbonyl, Het^2carbonyloxyalkyl, Het^2alkylcarbonyloxyalkyl, Het^2aralkylcarbonyloxyalkyl, cyano, $CR^3{=}NR^4$, $CR^3{=}N(OR^4)$, aminocarbonyl, aminoalkanoyl, aminoalkyl, optionally substituted by one or more substituents independently selected from the group comprising alkyl, aralkyl, aryl, Het^1, Het^2, cycloalkyl, alkyloxy, alkyloxycarbonyl, carboxyl, aminocarbonyl, mono- or di(alkyl)aminocarbonyl, aminosulfonyl, alkyl$S(=O)_t$, hydroxy, cyano, halogen or amino optionally mono- or disubstituted wherein the substituents are independently selected from the group comprising alkyl, aryl, aralkyl, aryloxy, arylamino, arylthio, aryloxyalkyl, arylaminoalkyl, aralkoxy, alkylthio, alkoxy, aryloxyalkoxy, aylaminoalkoxy, aralkylamino, aryloxyalkylamino, arylaminoalkylamino, arylthioalkoxy, arylthioalkylamino,

aralkylthio, aryloxyalkylthio, arylaminoalkylthio, arylthioalkylthio, alkylamino, cycloalkyl, cycloalkylalkyl, Het^1, Het^2, Het^1alkyl, Het^2alkyl, Het^1amino, Het^2amino, Het^1alkylamino, Het^2alkylamino, Het^1thio, Het^2thio, Het^1alkylthio, Het^2alkylthio, Het^1oxy and Het^2oxy, OR^3, SR^3, $SO_2NR^3R^4$, $SO_2N(OH)R^3$, CN, $CR^3{=}NR^4$, $S(O)R^3$, SO_2R^3, $CR^3{=}N(OR^4)$, N_3, NO_2, NR^3R^4, $N(OH)R^3$, $C(O)R^3$, $C(S)R^3$, CO_2R^3, $C(O)SR^3$, $C(O)NR^3R^4$, $C(S)NR^3R^4$, $C(O)N(OH)R^4$, $C(S)N(OH)R^3$, $NR^3C(O)R^4$, $NR^3C(S)R^4$, $N(OH)C(O)R^4$, $N(OH)C(S)R^3$, $NR^3CO_2R^4$, $NR^3C(O)NR^4R^5$, and $NR^3C(S)NR^4R^5$, $N(OH)CO_2R^3$, $NR^3C(O)SR^4$, $N(OH)C(O)NR^3R^4$, $N(OH)C(S)NR^3R^4$, $NR^3C(O)N(OH)R^4$, $NR^3C(S)N(OH)R^4$, $NR^3SO_2R^4$, $NHSO_2NR^3R^4$, $NR^3SO_2NHR^4$, $P(O)(OR^3)(OR^4)$, wherein t is an integer between 1 and 2 and R^3, R^4 and R^5 are each independently selected from the group comprising hydrogen, hydroxyl, alkyl, alkenyl, alkynyl, aminoalkyl, aminoaryl, alkylcarbonylamino, arylcarbonylamino alkylthiocarbonylamino and arylthiocarbonylamino;

wherein X_3 participates together with X_3' to an oxo functional group, or wherein X_3 is selected from the group comprising hydrogen, hydroxyl, sulfur, oxyalkyl, oxycarbonyl, alkyl, Het^1alkyl, alkenyl, alkynyl, aminoalkyl, aminoacyl, alkylcarbonylamino, alkylthiocarbonylamino, alkyloxycarbonyl optionally substituted by one or more substituents independently selected from the group comprising alkyl, aralkyl, aryl, Het^1, Het^2, cycloalkyl, alkyloxy, alkyloxycarbonyl, carboxyl and aminocarbonyl; and X_3' is selected from the group comprising hydrogen, alkyl, aryl, aralkyl, and optionally substituted by one or more substituents independently selected from the group comprising alkyl, aralkyl, aryl, Het^1, Het^2, cycloalkyl, alkyloxy, alkyloxycarbonyl, carboxyl, aminocarbonyl, mono- or di(alkyl)aminocarbonyl, aminosulfonyl, $alkylS(=O)_t$, hydroxy, cyano, halogen or amino optionally mono- or disubstituted wherein the substituents are independently selected from the group comprising alkyl, aryl, aralkyl, aryloxy, arylamino, arylthio, aryloxyalkyl, arylaminoalkyl, aralkoxy, alkylthio, alkoxy, aryloxyalkoxy, aylaminoalkoxy, aralkylamino, aryloxyalkylamino, arylaminoalkylamino, arylthioalkoxy, arylthioalkylamino, aralkylthio, aryloxyalkylthio, arylaminoalkylthio, arylthioalkylthio, alkylamino, cycloalkyl and cycloalkylalkyl;

wherein X_4 and X_7 are independently selected from the group comprising hydrogen, halogen, oxygen, oxo, carbonyl, thiocarbonyl, hydroxyl, alkyl, aryl, Het^1alkyl, Het^1aryl, alkenyl, alkynyl, hydroxyalkyl, hydroxycarbonyl, hydroxycarbonylalkyl, hydroxycarbonylaryl, hydroxycarbonyloxyalkyl and hydroxycarbonyloxyaryl; aminocarbonyl, mono- or di(alkyl)aminocarbonyl, aminosulfonyl, $alkylS(=O)_t$, hydroxy, aminoalkyl, aminoaryl, cyano, halogen or amino optionally mono- or disubstituted wherein the substituents are independently selected from the group comprising alkyl, aryl, aralkyl, aryloxy, arylamino, arylthio, aryloxyalkyl, arylaminoalkyl, aralkoxy, alkylthio, alkoxy, aryloxyalkoxy, aylaminoalkoxy, aralkylamino, aryloxyalkylamino, arylaminoalkylamino,

arylthioalkoxy, arylthioalkylamino, aralkylthio, aryloxyalkylthio, arylaminoalkylthio, arylthioalkylthio, alkylamino, Het^1, Het^2, alkyloxycarbonyl, carboxyl, aminocarbonyl, cycloalkyl and cycloalkylalkyl,

wherein X_5 participates to a double bond between the carbon atoms in position 4 and 5 or between carbon atoms in position 5 and 6, and X_6 is independently selected from the group comprising hydrogen, hydroxyl and hydroxyalkyl, or wherein X_5 and X_6 are independently selected from the group comprising halogen, hydrogen, hydroxyl, hydroxyalkyl, aminoalkyl, aminoaryl, optionally substituted by one or more substituents independently selected from the group comprising alkyl, aralkyl, aryl, Het^1, Het^2, cycloalkyl, alkyloxy, alkyloxycarbonyl, carboxyl, aminocarbonyl, and

wherein n is an integer between 0 and 10.

In a preferred embodiment, the present invention relates to a compound having the structural formula IA or IB or a pharmaceutically acceptable salt thereof as indicated above

wherein X_1, X_2, R_1 and R_2 is selected from the group comprising hydrogen, hydroxyl, oxyalkyl, oxo, alkyl, alkenyl, alkynyl, alkyloxy, alkyloxyalkyl, alkylthioalkyl, alkoxycarbonyl, alkylthiocarbonyl, alkanoyl, cycloalkylalkyl, cycloalkylcarbonyl, cycloalkylalkanoyl, cycloalkylthiocarbonyl, cycloalkylalkoxycarbonyl, cycloalkylalkoxythiocarbonyl, cycloalkylthioalkyl, alkylcarbonyloxyalkyl, cycloalkylcarbonyloxyalkyl, silyloxyalkyl, aralkyl, arylalkenyl, arylcarbonyl, aryloxycarbonyl, arylthiocarbonyl, aralkoxycarbonyl, arylalkylthiocarbonyl, aryloxyalky, arylthioalkyl, haloalkyl, hydroxyalkyl, aralkanoyl, aroyl, aryloxycarbonylalkyl, aryloxyalkanoyl, carboxyl, alkenylcarbonyl and alkynylcarbonyl;

wherein X_3 participates together with X_3' to an oxo functional group, or wherein X_3 is selected from the group comprising hydrogen, hydroxyl, sulfur, oxyalkyl, oxycarbonyl alkyl, Het^1alkyl, alkenyl, alkynyl, aminoalkyl, aminoacyl, alkylcarbonylamino, alkylthiocarbonylamino, alkyloxycarbonyl optionally substituted by one or more substituents independently selected from the group comprising alkyl, aralkyl, aryl, Het^1, Het^2, cycloalkyl, alkyloxy, alkyloxycarbonyl, carboxyl and aminocarbonyl; and X_3' is selected from the group comprising hydrogen, alkyl, aryl, aralkyl;

wherein X_4 and X_7 are independently selected from the group comprising hydrogen, oxygen, oxo, carbonyl, thiocarbonyl, hydroxyl, alkyl, aryl, Het^1alkyl, Het^1aryl, alkenyl, alkynyl, hydroxyalkyl, hydroxycarbonyl, hydroxycarbonylalkyl, hydroxycarbonylaryl, and hydroxycarbonyloxyalkyl;

wherein X_5 participates to a double bond between the carbon atoms in position 4 and 5 or between carbon atoms in positions 5 and 6, and X_6 is independently selected

from the group comprising hydrogen, hydroxyl, and hydroxyalkyl, or wherein X_5 and X_6 are independently selected from the group comprising hydrogen, hydroxyl, hydroxyalkyl, aminoalkyl, aminoaryl, optionally substituted by one or more substituents independently selected from the group comprising alkyl, aralkyl, aryl, Het^1, Het^2, cycloalkyl, alkyloxy, alkyloxycarbonyl, carboxyl, aminocarbonyl, and

wherein n is an integer between 0 and 5.

In another more preferred embodiment, the present invention relates to a compound having the structural formula IA or IB or a pharmaceutically acceptable salt thereof as indicated above

wherein X_1, X_2, R_1 and R_2 is selected from the group comprising hydrogen, hydroxyl, alkyloxy, oxo and oxyalkyl,

wherein X_3 participates together with X_3' to an oxo functional group, or wherein X_3 is selected from the group comprising hydrogen, hydroxyl, oxyalkyl, oxycarbonyl, and X'_3 is selected from the group comprising alkyl, aryl and aralkyl;

wherein X_4 and X_7 are independently selected from the group comprising hydrogen, oxygen, oxo and hydroxyl;

wherein X_5 and X_6 are hydrogen or wherein X_5 participates to a double bond between the carbon atoms in position 4 and 5, and X_6 is hydrogen, and

wherein n is an integer between 0 and 2.

In yet another more preferred embodiment, the present invention relates to a compound having the structural formula IA or IB or a pharmaceutically acceptable salt thereof as indicated above,

wherein X_1, X_2, X_3, X_3', X_6, X_7, R_1, R_2 and n are selected from the group indicated in claims 1 to 3; and

wherein X_4 is equal to X_5 and is selected from the group comprising halogen, aminoalkyl, aminoaryl, optionally substituted by one or more substituents independently selected from the group comprising alkyl, aralkyl, aryl, Het^1, Het^2, cycloalkyl, alkyloxy, alkyloxycarbonyl, carboxyl and aminocarbonyl, or wherein X_5 participates to a double bond between the carbon atoms in position 5 and 6, and X_4 is independently selected from the group comprising hydrogen, aminoalkyl, aminoaryl, optionally substituted by one or more substituents independently selected from the group comprising alkyl, aralkyl, aryl, Het^1, Het^2, cycloalkyl, alkyloxy, alkyloxycarbonyl, carboxyl and aminocarbonyl.

In another preferred embodiment the present invention relates to a compound having the structural formula IA or IB or a pharmaceutically acceptable salt thereof as indicated above wherein X_1, X_2, X_3, X_3', X_6, X_7, R_1, R_2 and n are selected as indicated above; and

wherein X_5 may form with X_6 a single bond when X_5 or X_6 represents an oxygen atom thereby forming an -O- functional group.

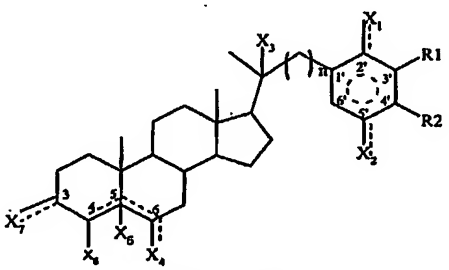
In a preferred embodiment the present invention relates to a compound having the structural formula IA or a pharmaceutically acceptable salt thereof as indicated above, wherein X_1 and X_2 are –OMe, wherein R_1 and R_2 are –H, wherein X_3 is –OH, wherein X_4 is hydrogen, wherein X_5 participates to a double bond between the carbon atoms in position 5 and 6, wherein X_6 is –H, wherein X_7 is hydroxyl and wherein n is 0.

In another preferred embodiment the present invention relates to a compound having the structural formula IB or a pharmaceutically acceptable salt thereof as indicated above, wherein X_1 and X_2 are –OMe, wherein R_1 and R_2 are –H, wherein X_4 and X_7 are oxo, wherein X_3 participates together with X_3' to an oxo functional group, wherein X_5 participates to a double bond between the carbon atoms in position 4 and 5, wherein X_6 is hydrogen, and wherein n is 0.

In yet another preferred embodiment the present invention relates to a compound having the structural formula IA or a pharmaceutically acceptable salt thereof as indicated above, wherein X_1 and X_2 are –OMe, wherein R_1 and R_2 are –H, wherein X_4 and X_7 are oxo, wherein X_3 is -OH, wherein X_5 participates to a double bond between the carbon atoms in position 4 and 5, wherein X_6 is hydrogen, and wherein n is 0.

In yet another embodiment the present invention relates to a compound having the structural formula IA or IB or a pharmaceutically acceptable salt thereof as indicated above, wherein X_1, X_2, X_3, X_3', X_4, X_5, X_6, X_7, R_1, R_2 and n are selected as indicated in Table A or Table B.

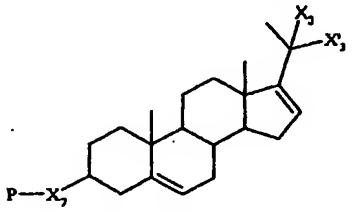
In another embodiment, the present invention relates to a method for synthesizing a compound having the structural formula IA,



formula IA

wherein X_1, X_2, X_3, X_4, X_5, X_6, X_7, R_1, R_2 and n are selected from the group as indicated in any of claims 1 to 9, said method comprising the steps of

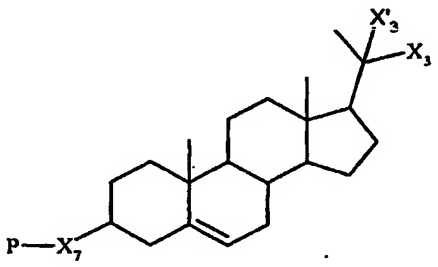
a) providing a starting material having the structural formula IV,



formula IV

wherein X_3, X_3' and X_7 are selected from the group as indicated above, and wherein P is a protecting group,

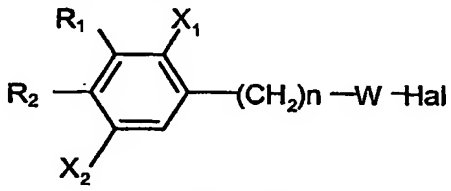
(b) hydrogenating the compound of step a) thereby obtaining a compound having the structural formula III'A



formula III'A

wherein X_3, X_3' and X_7 are selected from the group as indicated above, and wherein P is a protecting group,

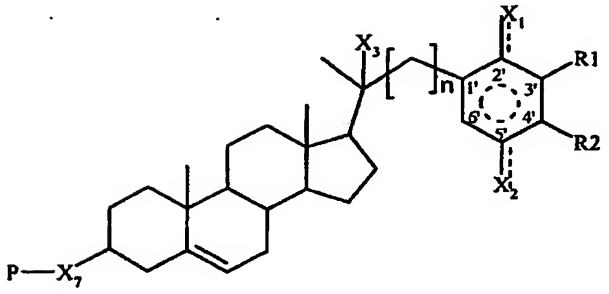
c) effecting reaction between the compound of step b) with an organometallic compound having the structural formula V



formula V

wherein X_1, X_2, R_1, R_2 and n are selected from the group as indicated above, wherein W is a metal or a combination of metals and wherein Hal is a halogen atom,

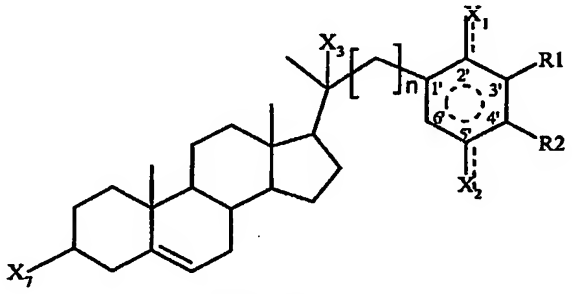
to result in an intermediate having the structural formula IIIA



formula IIIA

wherein X_1, X_2, X_3 , X_7 R_1, R_2 and n are selected from the group as indicated above, and wherein P is a protecting group,

d) deprotecting the X_7 group of the compound obtained in step c) to form an intermediate having the structural formula IIA

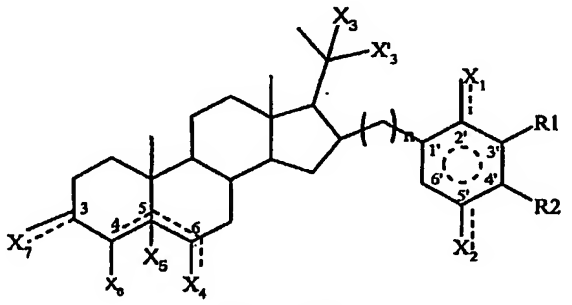


formula II A

wherein X_1, X_2, X_3 , X_7 R_1, R_2 and n are selected from the group as indicated above, and

e) oxidizing by reaction with a suitable oxidizing agent or agents to form a compound of formula IA.

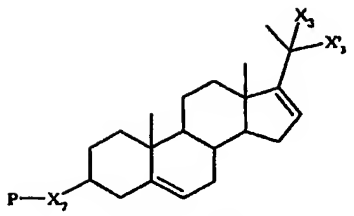
In yet another embodiment the present invention relates to a method for synthesizing a compound having the structural formula IB



formula IB

wherein X_1, X_2, X_3, X_4, X_5, X_6, X_7, R_1, R_2 and n are selected from the group as indicated above, said method comprising the steps of

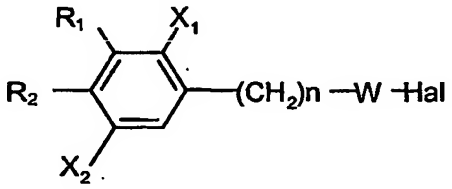
a) providing a starting material having the structural formula IV,



formula IV

wherein X_3, X_3' and X_7 are selected from the group as indicated above, and wherein P is a protecting group,

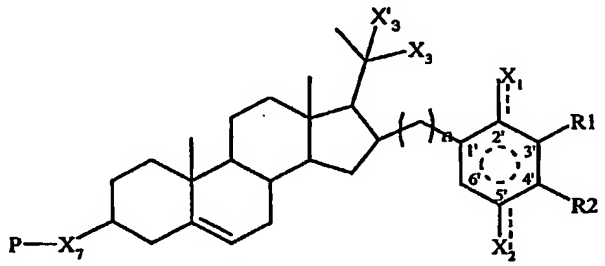
(b) effecting reaction between the compound of step a) with an organometallic compound having the structural formula V



formula V

wherein X_1, X_2, R_1, R_2 and n are selected from the group as indicated above, wherein W is a metal or a combination of metals and wherein Hal is a halogen atom,

to result in an intermediate having the structural formula III'B



formula III'B

wherein X_1, X_2, X_3, X_3', X_7, R_1, R_2 and n are selected from the group as indicated above, and wherein p is a protecting group,

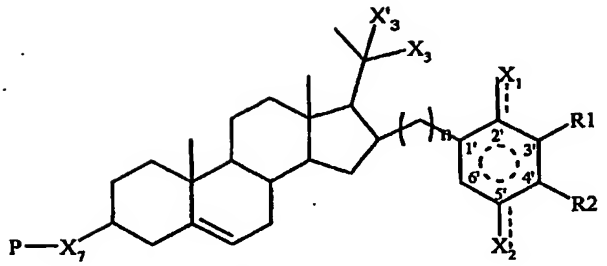
c) effecting reaction between the compound of step b) with an organometallic compound having the structural formula VI

HAL-W-X'$_3$

formula VI

wherein X'$_3$ is selected from the group as indicated above, wherein W is a metal or a combination of metals, and wherein Hal is a halogen atom,

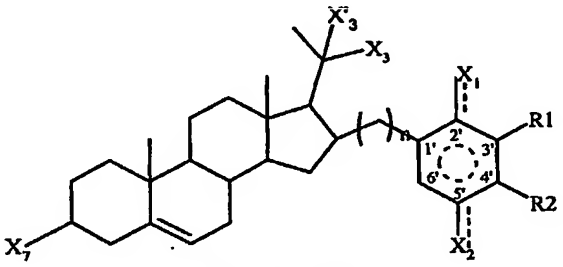
to result in an intermediate having the structural formula IIIB



formula IIIB

wherein X_1, X_2, X_3, X_3', X_7, R_1, R_2 and n are selected from the group as indicated above, wherein P is a protecting group,

d) deprotecting the X_7 group of the compound obtained in step c) to form an compound having the structural formula IIB



formula II B

wherein X_1, X_2, X_3, X_3', X_7, R_1, R_2 and n are selected from the group as indicated above, and

e) oxidizing by reaction with a suitable oxidizing agent or agents to from a compound of formula IB.

In another embodiment the present invention further relates to a compound obtainable by any of the steps according to the method for synthesizing a compound having the structural formula IA as indicated above.

In yet another embodiment the present invention further relates to a compound obtainable by any of the steps according to the method for synthesizing a compound having the structural formula IB as indicated above.

In a preferred embodiment, the present invention provides a compound designated as compound UBS1740 as described in the specification.

In another preferred embodiment, the present invention provides a compound designated as compound UBS1664 as described in the specification.

In yet another preferred embodiment, the present invention provides a compound designated as compound UBS1819 as described in the specification.

In still another preferred embodiment, the present invention provides a compound designated as compound UBS 881 as described in the specification.

In another embodiment, the present invention provides a compound as indicated above for use as a medicament.

In a further embodiment, the present invention relates to the use of a compound as indicated above for the preparation of a medicament for treating cancer.

In yet another further embodiment, the invention concerns a pharmaceutical composition comprising a pharmaceutically acceptable excipient and a therapeutically effective amount of a compound as indicated above.

The present invention further relates in another embodiment to the use of a pharmaceutical composition as indicated above in the treatment of cancer.

In addition, in yet another embodiment, the present invention provides a method of treating cancer comprising administrating to an individual in need of such treatment a pharmaceutical composition as indicated above.

STEROID COMPOUNDS WITH ANTI-TUMOR ACTIVITY

ABSTRACT

The present invention relates to novel steroid compounds having anti-tumor activity. The present invention also relates to a method for the preparation of said steroid compounds. The invention further relates to a pharmaceutical composition comprising an effective amount of said steroid compounds. Furthermore, the present invention concerns the use of said steroid compounds as a medicament and in the preparation of a medicament for the treatment of cancer. The present invention also relates to the use of a steroid compound or a pharmaceutical composition comprising said steroid compound according to the invention in the treatment of cancer.

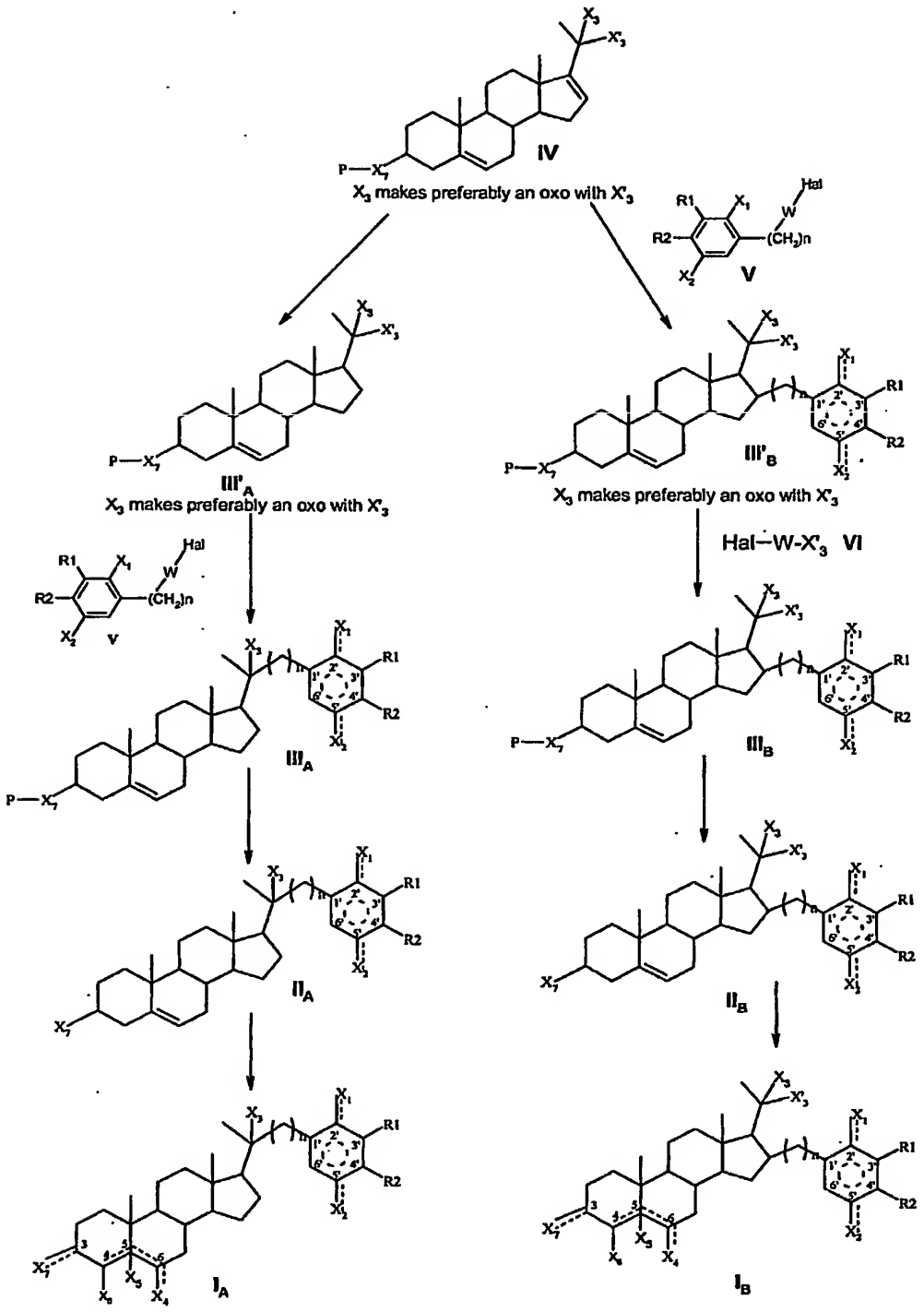

IV
X3 makes preferably an oxo with X'3
V
III'A
X3 makes preferably an oxo with X'3
III'B
X3 makes preferably an oxo with X'3
Hal—W-X'3 VI
V
IIIA
IIIB
IIA
IIB
IA
IB

Fig. 1

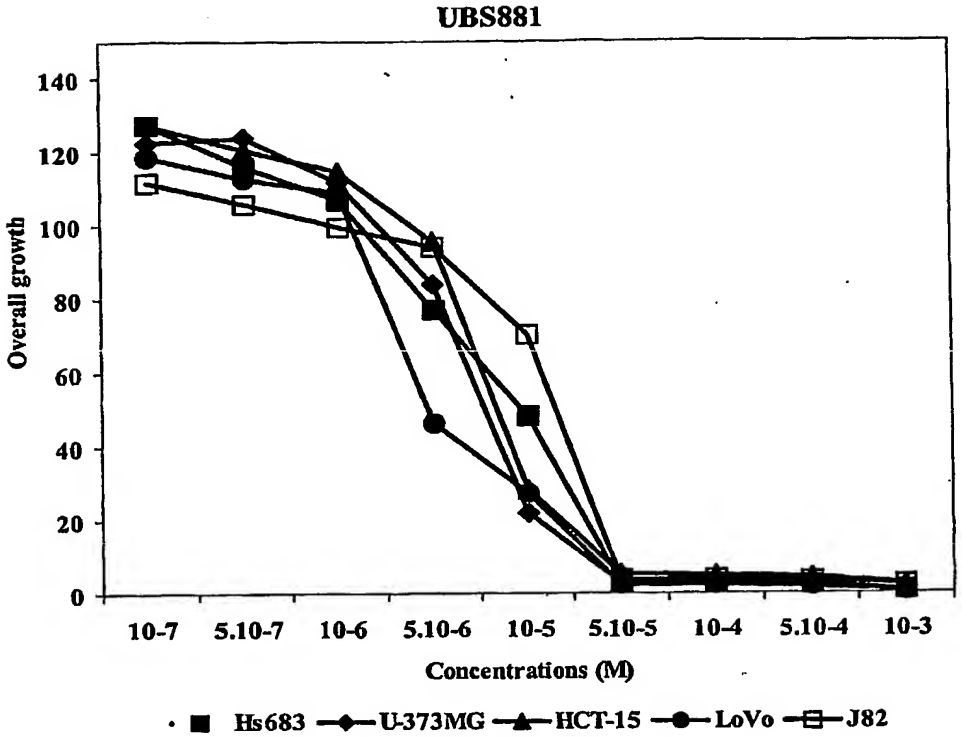
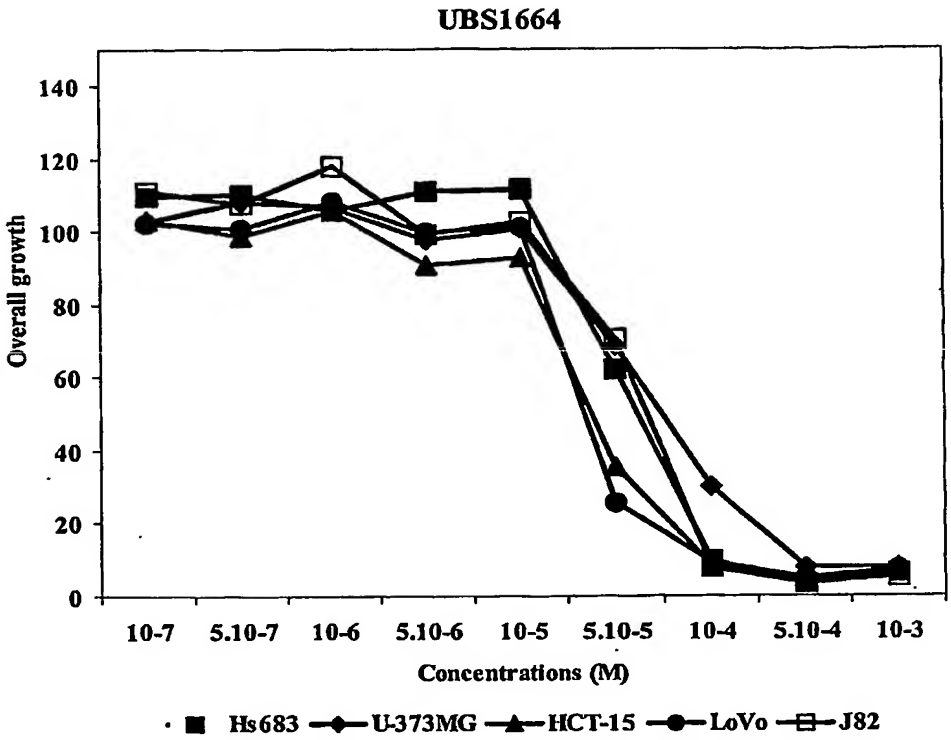

UBS881
Overall growth
140
120
100
80
60
40
20
0
10-7
5.10-7
10-6
5.10-6
10-5
5.10-5
10-4
5.10-4
10-3
Concentrations (M)
Hs683
U-373MG
HCT-15
LoVo
J82

Fig. 2


UBS1664
Overall growth
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120
100
80
60
40
20
0
10-7
5.10-7
10-6
5.10-6
10-5
5.10-5
10-4
5.10-4
10-3
Concentrations (M)
Hs683
U-373MG
HCT-15
LoVo
J82

Fig. 3

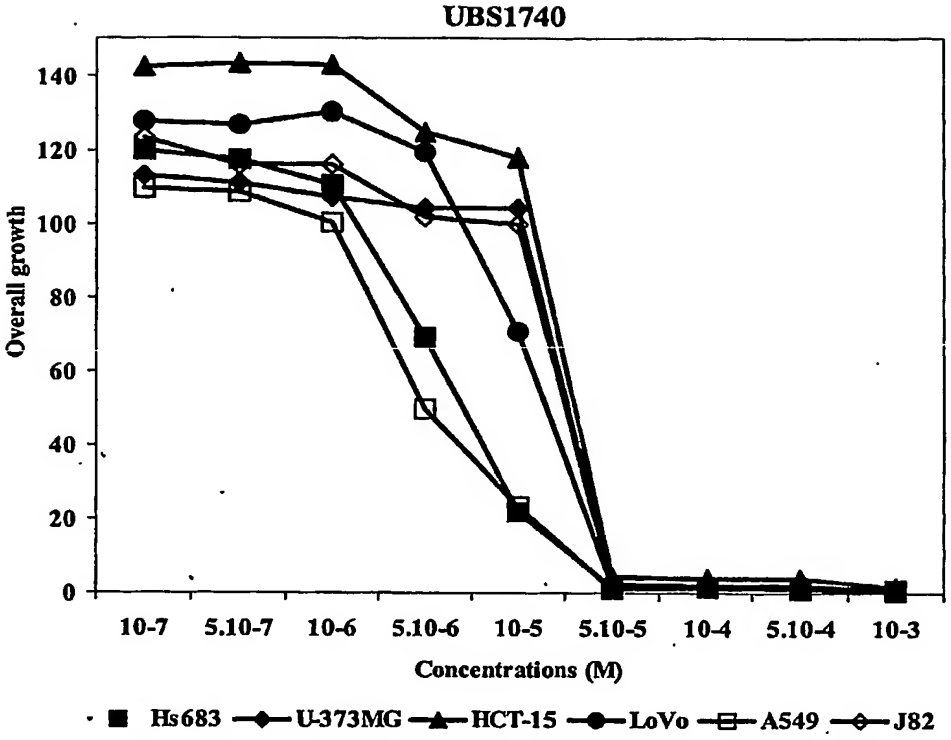
UBS1740
Overall growth
140
120
100
80
60
40
20
0
10-7
5.10-7
10-6
5.10-6
10-5
5.10-5
10-4
5.10-4
10-3
Concentrations (M)
Hs683
U-373MG
HCT-15
LoVo
A549
J82

Fig. 4

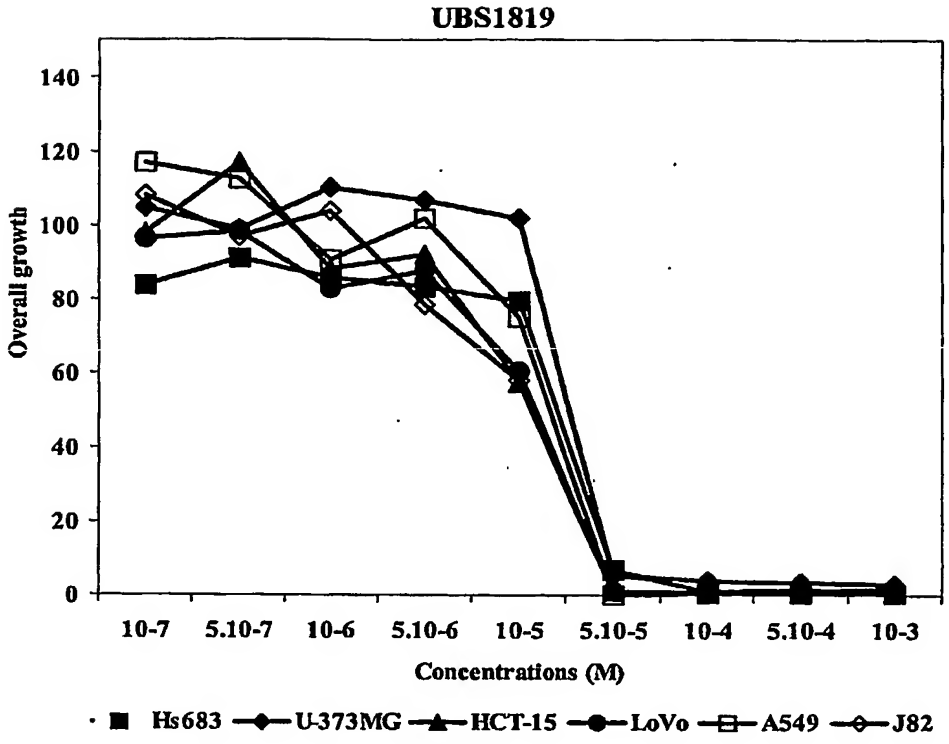
UBS1819
Overall growth
140
120
100
80
60
40
20
0
10-7
5.10-7
10-6
5.10-6
10-5
5.10-5
10-4
5.10-4
10-3
Concentrations (M)
Hs683
U-373MG
HCT-15
LoVo
A549
J82

Fig. 5

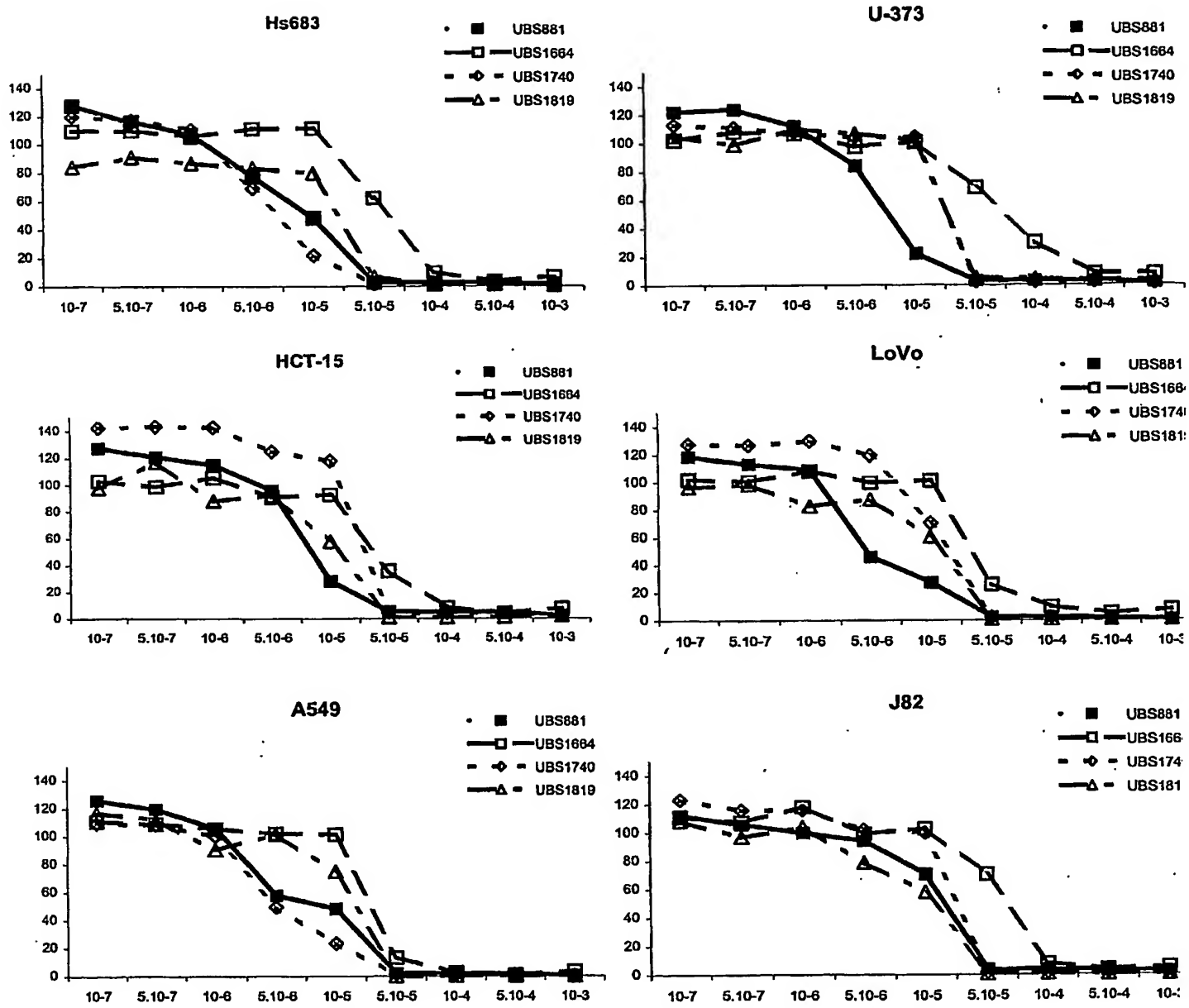
Hs683
U-373
HCT-15
LoVo
A549
J82
UBS881
UBS1664
UBS1740
UBS1819
140
120
100
80
60
40
20
0
10-7
5.10-7
10-6
5.10-6
10-5
5.10-5
10-4
5.10-4
10-3

Fig. 6